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OBSERVATIONS ON THE PATHOLOGY OF EXPERIMENTAL TRAUMATIC SHOCK

J. ENGLEBERT DUNPHY, M.D., JOHN G. GIBSON, II, M.D.,
Boston, Massachusetts
JOHN L. KEELEY, M.D., New Orleans, Louisiana

An essential feature of the shock syndrome is a disparity between the amount of circulating blood and the size of the vascular bed (1, 5, 14, 17). In traumatic shock, this disparity is the result of a marked reduction of the blood volume as a result of a loss of fluid from the circulation into the tissues. However, except in instances of frank hemorrhage, there is still considerable disagreement as to the actual site of this loss of fluid. Some investigators maintain that it is largely confined to the site of injury whereas others hold that, as a consequence of generalized capillary injury, there is a stasis of fluid and loss of plasma throughout the body, particularly marked in the splanchnic area. In the present study an attempt is made to throw further light on this problem by correlating more closely the physiological with the pathological changes in traumatic shock.

In keeping with the concept of generalized capillary injury as a principal factor in the shock syndrome are the extensive studies of Moon and his associates on the pathological changes in shock (11–14). These investigators find as an invariable accompaniment of shock, regardless of cause, "marked diffuse congestion of the capillaries and venules in visceral areas, especially the lungs, liver, kidneys, and the serous and mucous surfaces; edema, effusions into serous cavities and capillary hemorrhages" (12). The pathological changes are interpreted as evidence that the marked reduction of the blood volume is due to a loss of plasma and stasis of fluid throughout the viscera, particularly in the lungs, liver, and gastro-intestinal tract. Moon's investigations have done much to revive the theory of a traumatic toxemia in shock and are considered to be evidence against the idea of Blalock and others that in traumatic shock loss of fluid at the site of injury is a principal factor in the reduction of the blood volume (2, 3, 4, 9, 10, 15, 16).

Although Moon's observations clearly demonstrated that certain pathological changes may accompany shock, the causal relationship between these changes and the reduction of the blood volume was not shown. It seemed possible that in traumatic shock the primary mechanism was a loss of fluid, not blood, at the site of injury with an initial reduction of the blood volume, and that the generalized capillary change was a phenomenon secondary to the reduction of the blood volume. To determine this point, traumatic shock was

From the Laboratory for Surgical Research, Harvard Medical School and the Surgical and Medical Services of the Peter Bent Brigham Hospital.

TABLE I

Experiment	Hours after injury	Wt. kg.	Total blood volume	Plasma volume	Hematocrit	Pulse	Respirations	Blood press. sys.	Pathological findings
Thermal Trauma									
5	Control	24.4	2140	1200	43.8	130	10	157	Gross examination: There was extensive edema and swelling at the site of injury. The dependent portions of the lungs were a purplish red color and appeared congested and atalectatic. There were hemorrhages and ulcerations in the intestines. Microscopically there was evidence of generalized capillary injury in the lungs, liver, kidneys, adrenals, and gastro-intestinal tract
	3		1680	880	47.6	168	18	140	
	14	23.8	1420	592	58.3	240	36	74	
6	Control	25.8	2300	1208	40.8	108	10	120	Essentially as in Exp. 5
	5	25.3	1395	695	50.2	168	16	128	
	10	24.8	1190	590	53.4	200	34	40	
7	Control	28.9	2295	1170	50.5	72	13	132	Essentially the same microscopic changes
	3		1770	715	62.3	158	14	110	
	14	27.4	1580	543	67.7	234	32	54	
8	Control	24.1	2270	1050	55.0	120	17	140	Essentially the same microscopic changes
	4	23.4	2005	875	56.5	142		120	
	10	23.2				214		120	
9	Control	22.5	1900	1090	45.	167	8	150	Animal sacrificed 9 hours after injury. Pathological examination showed marked loss of fluid at site of injury and moderate amount of generalized capillary injury
	3		1500	700	57.	200	20	160	
	7		1445	675	57.	200	24	160	
	9					210	26	180	
10	Control	27.8	3700	2050	45.	150		140	This was an unusually severe injury. The animal died at the end of 6 hours. Pathological examination showed extensive local loss of fluid, but generalized changes were less marked than in the longer experiments
	6	26.4	2800	1500	49.	250		50	
11	Control	25.4	2200	1150	49.	80	16	120	Early stage of shock. Gross examination showed little variation from the normal (Fig. 4). Microscopic changes insufficient to account for reduction of blood volume. See text for details
	½		2200	1150	50.	140	18	120	
	1		1650	700	54.	140	18	115	
	5		1600	700	55.	180	18	120	
12	Control	17.4	1800	900	51.	140	10	100	Early stages of shock. Pathological examination disclosed no striking variation from normal. See text for details
	2½		1700	600	56.	200	24	110	
	5		1600	600	57.	200	20	100	
16	Control	20.6	—	—	45.	140	22	140	Early stages of shock. Pathological examination disclosed no striking variation from the normal
	4	20.2	2	—	51.	160	20	136	
Mechanical Trauma									
17	Control	20.6	1810	1018	43.7	160	14	138	Early stages of shock, following mechanical trauma. Pathological examination showed no striking variation from the normal (Fig. 5)
	¾		1830	1060	42.2	180	10	100	
	4	20.1	1300	693	47.	200	16	120	
18	Control	21.7	1650	755	53.2	150	12	100	Early shock. This dog was more affected by the anesthetic than usual. Note the higher initial hematocrit. Pathological examination disclosed slightly more evidence of generalized capillary injury than usual. The spleen had not been removed
	1		1645	706	47.1	160	10	120	
	3′ 54″		1730	695	60.	164	14	110	
19	Control	28.5	—	—	52.	135	20	160	Pathological changes showed evidence of generalized capillary injury. Not as marked as that seen following thermal trauma
	9		—	—	62.	180	20	130	

produced in animals and complete pathological examination of the viscera was made in different animals at varying intervals during the development of the shock syndrome as evidenced by determination of the blood volume, plasma volume, hematocrit, and blood pressure.

EXPERIMENTAL PROCEDURE

The experimental procedure was as follows: Large mongrel dogs, weighing between 18 and 28 kilograms, were used in all the experiments. Shock was induced either by severe burns or by trauma to the left hind limb. Animals were allowed water but no food for 24 hours before the experiment. Anesthesia was induced by the intravenous injection of sodium pentobarbital in doses of 32 milligrams per kilogram of body weight, and maintained by small supplementary injections throughout the experimental period. Determinations of the blood pressure, pulse, respiration, hematocrit, plasma, and total blood volumes were made before and at varying intervals after the

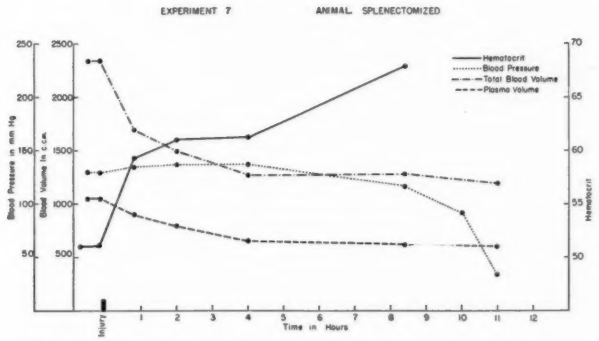

Fig. 1. The course of the changes in hematocrit, blood pressure, plasma, and total blood volumes in an animal following severe thermal trauma.

injury. The plasma and blood volumes were determined by the direct method of Gibson and Evans. The blood pressure was recorded on a Harvard kymograph by means of a cannula in the right femoral artery. Three animals were subjected to mechanical trauma to the left hind limb, administered with a heavy padded hammer in such a manner as to avoid fracturing bones or rupturing large blood vessels. Nine animals were subjected to thermal trauma by means of a Bunsen burner applied for periods of 5 to 20 minutes to shaven areas over the thorax and abdomen, constituting approximately one-third of the surface area of the animal's body. As soon as the experiment was terminated, a complete postmortem examination was performed and sections of the thoracic and abdominal viscera were taken for microscopic study. From all but 3 of the animals (Exp. 12, 17, 18) the spleen was removed several weeks before the experiment. This was done because previous observations indicated that shock could be produced more readily and more uniformly in the splenectomized dog (10).

Since the changes in the hematocrit, blood pressure, plasma, and total blood volume were quite uniform (Table I), one of the experiments is illustrative (Fig. 1). It will be noted that within a few hours of the injury there is marked hemoconcentration. Although the plasma blood volume is reduced to nearly two-thirds of its original total, the blood pressure is maintained well above so called "shock levels." At this early stage of shock, when the blood volume was markedly reduced but the blood pressure was well maintained, the experiment was terminated in 5 instances (Exp. 11, 12, 16, 17, 18) by the injection of a lethal dose of the anesthetic. The course of an experiment which was so terminated is shown in Figure 2. This animal was subjected to repeated trauma to the left hind limb. The rise in the hematocrit is an indication of shock rather than hemorrhage. The details of one experiment in which the animal was sacrificed in the early stages of shock are shown in Table II.

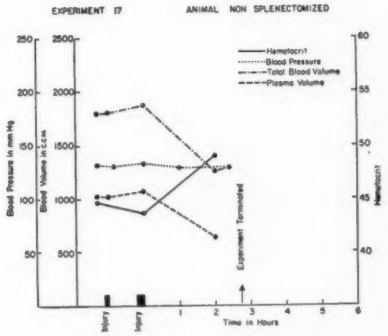

Fig. 2. The course of the changes in hematocrit, blood pressure, plasma, and total blood volume following mechanical trauma to the left hind limb. The experiment was terminated by a lethal dose of the anesthetic. The viscera of this animal are shown in Figure 5.

TABLE II.—ANIMAL SACRIFICED IN EARLY STAGES OF SHOCK—PROTOCOL: ANIMAL No. 160-39. EXPERIMENT 17. WEIGHT, 20.6 KILOGRAMS.

Time	Blood pressure	Pulse	Respirations	Total blood volume	Plasma volume	Hematocrit	Remarks
8:30 a.m.							Sodium pentobarbital 0.659 gm. injected intravenously
8:45 a.m.	140	140	14				Cannula in right femoral artery
10:10 a.m.	138	160	14	1810 c.cm.	1018 c.cm.	43.7	
10:20 a.m.							Animal light. Sodium pentobarbital 4 c.cm. intravenously
10:30 a.m.	138	160	12				
10:55 a.m.							Trauma to left hind limb
10:58 a.m.	125	170	12				
11:06 a.m.							Trauma repeated
11:10 a.m.	100	180	10				
11:30 a.m.				1830 c.cm.	1060 c.cm.	42.2	
12:00 a.m.	124	170	12				
12:03 p.m.							Trauma repeated for 2 minutes
12:05 p.m.	100	190	10				
1:30 p.m.	120	206	16				
2:25 p.m.	120	180	16				
3:00 p.m.				1300 c.cm.	693 c.cm.	47	
3:33 p.m.							Animal sacrificed; 30 cc. sodium pentobarbital.

Pathological examination: There is extensive swelling, ecchymosis and hemorrhage into the tissues of the left leg. The tissues of the abdominal wall appear normal. The peritoneal cavity contains no fluid, but the serous surfaces are moist. The intestinal tract is pale and contracted. The lungs are pink and well aerated. The heart is small and contracted. It contains a moderate amount of blood. No abnormalities are noted in the gross examination of the abdominal viscera (Fig. 5). Microscopically no evidence of generalized capillary damage is found.

THE PATHOLOGY OF EARLY SHOCK

Autopsy of animals sacrificed in the early stages of shock revealed marked loss of plasma and fluid at the site of injury but little or no evidence of generalized capillary injury or loss of fluid in the visceral area (Figs. 3, 4, 5). Gross inspection of the viscera showed no significant variation from the normal. There was no free fluid in the pleural or peritoneal cavities and the serous surfaces were dry. The heart appeared normal grossly and contained a moderate amount of blood. The lungs were a light pinkish yellow and were dry and crepitant throughout. The liver and kidneys showed no gross variation from the normal. The spleen, in the 3 animals in which it had not been removed prior to the experiment, was contracted and firm. The cut surface was dry and little pulp could be scraped off with a knife. The gastro-intestinal tract was often pale, contracted, and ischemic in appearance (Fig. 4). There was no increase present in the weight of the lungs, the liver, or the kidneys.

Histologically these observations were substantiated. In the lung (Fig. 6) there was no edema, extravasation of red blood cells or leucocytes, or marked engorgement of the alveolar capillaries. In scattered areas there was slight dilatation of capillaries and occasionally polymorphonuclear leucocytic infiltration of the interstitial tissue was found, a change which was quite marked in the late stages of shock. The liver showed no significant variation from normal (Fig. 7). There was no engorgement of the sinusoids, necrosis of the cord cells, capillary hemorrhage, or edema. A moderate number of the cord cells contained fat droplets. The gastro-intestinal tract was singularly free from edema, congestion, submucosal hemorrhages, or engorgement of the serosal vessels. There was no gross or microscopic congestion of the mesentery. The mucosa of the gastro-intestinal tract was well preserved (Fig. 8). Thus, in the initial stage of shock the changes in the viscera were more suggestive of hemorrhage than of what has been described as being typical of shock. The

Fig. 3. Photograph of the viscera of an animal 4 hours after thermal trauma. The lungs were prevented from collapsing by clamping off the trachea before opening the chest. There is no visceral congestion or effusion of fluid into serous cavities. The omentum is bloodless, and small bowel is pale and contracted. The spleen had been removed.

Fig. 4. Photograph of the viscera of an animal 5 hours after thermal trauma. Note that after the chest has been opened the lungs are completely collapsed against the chest wall. There is no congestion or edema of the lungs present nor is there any effusion into the pleural cavities (Exp. 12).

kidney was an exception. Although the extreme degrees of congestion described by Moon were not observed, there was slight hyperemia and congestion of the glomerular capillaries even in the early stages of shock. This was particularly striking after thermal trauma, a finding which was in keeping with the fact that gross hematuria was commonly observed within a short time of the injury.

The adrenals showed no striking variation from the normal on gross examination, but microscopically there was hyperemia of the capillaries and an infiltration of polymorphonuclear leucocytes in the zona fasciculata. These changes were not marked but were present in all the dogs of the series. They developed before there was evidence of generalized capillary congestion and engorgement of vessels throughout the viscera. In fact, at this stage the adjacent zona glomerulosa, zona reticularis, and medulla of the adrenal appeared quite normal despite the pathological changes in the zona fasciculata. In a previous study it was shown that these changes develop in the transplanted adrenal gland and hence are not of neurogenic origin (7).

The slight hyperemia of the pulmonary capillaries, the occasional infiltration of the interstitial tissue of the lung with polymorphonuclear leucocytes, the renal and the adrenal changes are interpreted as evidence that, under the conditions of our experiments, there are slight systemic tissue changes in early shock. The possible relation of these changes to the use of sodium pentobarbital as the anesthetic will be discussed later. However, re-

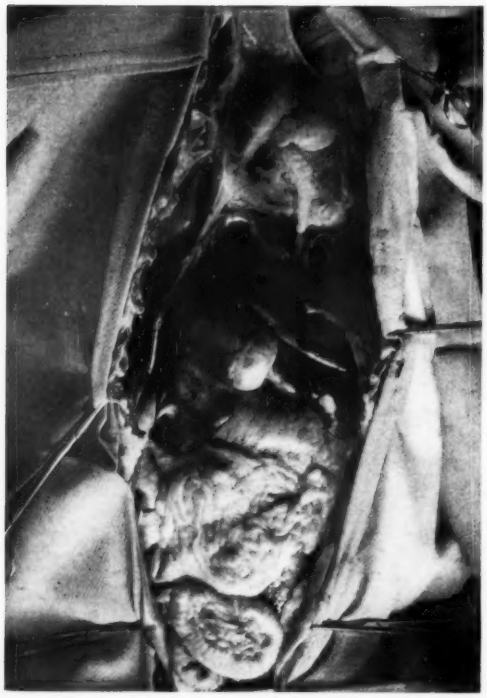

Fig. 5. Photograph of the viscera of an animal 4 hours after trauma to the left hind limb. The gross appearance of the viscera is not unlike that seen following hemorrhage. That this animal was in shock is shown by the rise in hematocrit (Fig. 2).

gardless of cause, these pathological changes are not sufficient to account for the marked reduction of the blood volume. Moreover, as will be shown later, they can be produced without a reduction of the blood volume. It is significant, therefore, that at this early stage of shock there was extensive swelling, edema, and extravasation of fluid at the site of injury. Furthermore, previous observations indicated that the calculated gain in fluid content of the injured area closely approximated the reduction of the blood volume (10). It is concluded that under the conditions of these experiments the principal loss of fluid in the early stages of traumatic shock is at the site of injury.

THE PATHOLOGY OF LATE SHOCK

In the experiments (Nos. 5, 6, 7, 8, 9, 10, 19) in which the animals were allowed to survive for longer periods of time—6 to 12 hours—or until death occurred, a somewhat different pathological picture was found. It is important to emphasize that inasmuch as shock depends upon the reaction of different animals to a variety of stimuli, standardization of experimental shock is difficult, and therefore the time factor in these experiments is not an absolute one. Certain animals develop the pathological changes of late shock in a shorter time than others. In general, however, the longer the animals survived, the more striking were the generalized tissue changes. The extreme degrees of generalized capillary injury, visceral congestion, and effusion into serous cavities described by Moon were not found in any of these experiments. However, microscopically, there was a definite change in that direction and in less acute experiments which permitted the animals to survive for longer periods of time, the changes might become more marked. The details of one experiment in which the animal was sacrificed in the later stages of shock are presented herein in Table III.

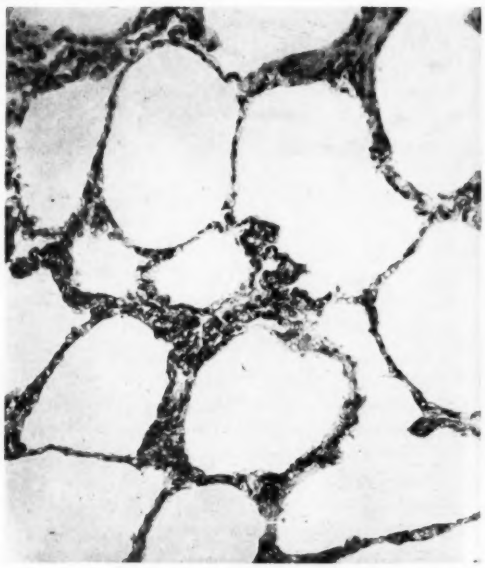

Fig. 6. Photomicrograph of the lungs of the same animal as in Figure 5. There is no edema or extravasation of red cells or engorgement of the alveolar capillaries. Hematoxylin-eosin stain. ×200.

Gross examination of the viscera in the late stages of shock, after compensation had failed and the blood pressure had fallen, showed patchy areas of purplish discoloration in the lungs, particularly in the lower lobes. Microscopically (Fig. 9) there was engorgement of the alveolar capillaries, extravasation of cells and fluid into the alveolar spaces, and infiltration of the interstitial tissues with polymorphonuclear leucocytes. No micro-organisms were demonstrated. In the gastro-intestinal tract there were varying degrees of hyperemia, submucosal hemorrhages, and occasionally ulcerations in the duodenum or jejunum. The mucosa was frequently poorly preserved and the small vessels of the bowel were markedly congested (Fig. 10, 11). The liver was deep purplish red, and the cut surface was soft and friable. Fluid and blood oozed from it when it was sectioned. On microscopic examination there was found dilatation and engorgement of capillaries, congestion of the sinusoids with red blood cells, and degenerative changes in the cord cells (Fig. 12). The kidneys appeared normal in size. On section, the demarcation of cortex and medulla was present, but the organ was deep purple, and a considerable amount of blood oozed from the cut surface. Microscopically, there was marked congestion of the glomerular capillaries, degenerative changes in the tubules, and extravasation of cells and engorgement of capillaries in the medulla.

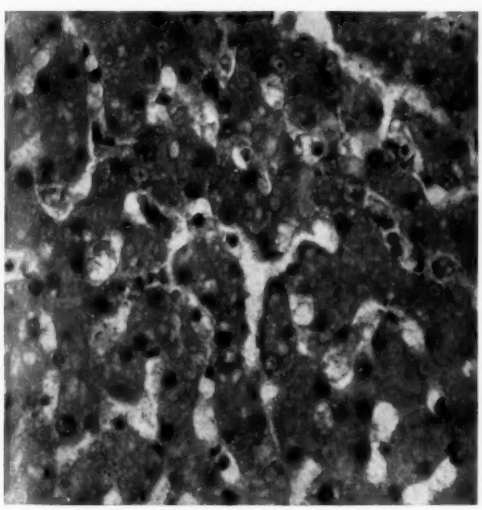

Fig. 7. Photomicrograph of the liver of an animal 4 hours after thermal trauma. There is a moderate number of fat droplets in the cord cells. There is no striking variation from the normal. Hemotoxylin-eosin stain. ×425.

Fig. 8. Photomicrograph of the jejunum of an animal 4 hours after thermal trauma. The epithelium is well preserved. There is no congestion, edema, or capillary hyperemia. Hemotoxylin-eosin stain. ×425.

The adrenals were pale white, but on section the cortex showed a reddish colored radial streaking as a result of hemorrhages. Microscopically there was swelling of the cortical cells in the zona fasciculata and a heavy infiltration of polymorphonuclear leucocytes. These changes were most marked in the zona fasciculata but to a lesser extent involved the zona reticularis and, in a few instances, the zona glomerulosa. There was also congestion and dilatation of the small vessels in both the cortex and medulla with occasional areas of hemorrhage. The significance of these changes

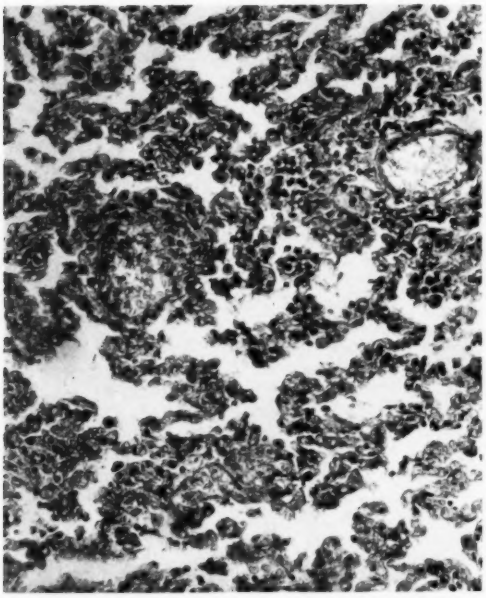

Fig. 9. Photomicrograph of the lung of an animal 12 hours after a severe burn. There is marked congestion of the alveolar capillaries and extravasation of cells and fluid into the alveolar spaces. Hemotoxylin-eosin stain. ×200.

in the adrenal gland is not clear, and their relationship to the shock syndrome is not established. As will be described later, such changes can be produced by the anesthesia alone without a significant reduction of the blood volume.

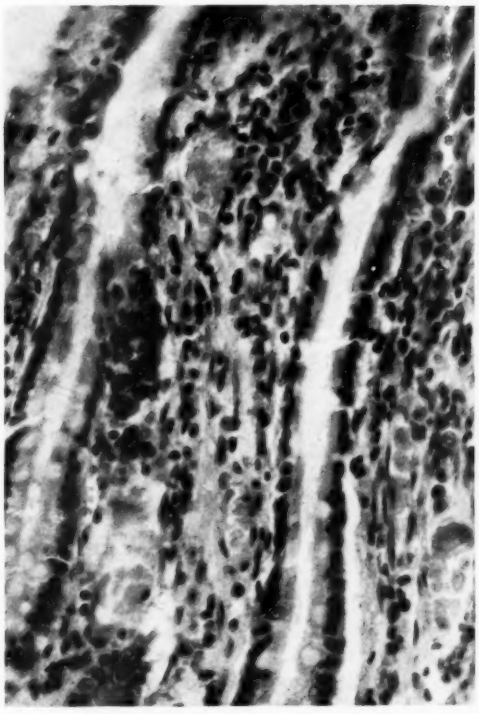

Fig. 10. Photomicrograph of a specimen of tissue removed from the jejunum of an animal 12 hours after the administration of thermal trauma. There is present marked engorgement of the small blood vessels and capillaries. Hemotoxylin-eosin stain. ×425.

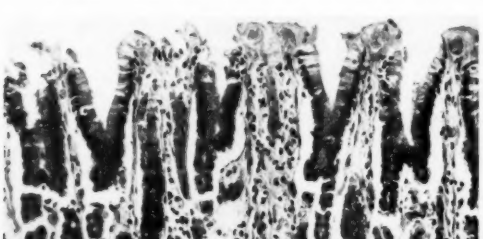

Fig. 11. Photomicrograph of the stomach of an animal 12 hours after thermal trauma showing extensive engorgement of capillaries and small vessels with red blood cells. Hemotoxylin-eosin stain. ×310.

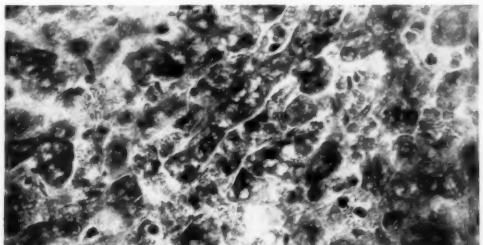

Fig. 12. Photomicrograph of liver of an animal 12 hours after thermal trauma. There are degenerative changes in the cord cells and engorgement of the sinusoids with fluid and red blood cells. Hemotoxylin-eosin stain. ×350.

TABLE III.—PROTOCOL: ANIMAL No. 204–38. EXPERIMENT 9. WEIGHT 22.5 KILOGRAMS

Time	Blood pressure	Pulse	Respirations	Total blood volume	Plasma volume	Hematocrit	Remarks
7:40 a.m.	160	160	9				Sodium pentobarbital 25 c.cm. injected intravenously. Abdomen, chest, and flanks shaved. Cannula inserted in right femoral artery. Catheter inserted in bladder. Left jugular vein exposed to facilitate taking samples of blood
8:50 a.m.	150	164	8	1900 c.cm.	1090	47	
9:15 a.m.							Cannula washed out.
9:21 a.m.							Thermal trauma to both sides of body for 10 minutes
9:32 a.m.	145	164	10				Sodium pentobarbital 3 c.cm. at 10.07 a.m.
10:15 a.m.	160						Washed out cannula
10:25 a.m.	160	198	20				
11:10 a.m.	160	180	20				Washed out cannula
12:00 a.m.							30 c.cm. dark, bloody urine aspirated from bladder
1:07 p.m.	160	200	20	1600 c.cm.	900	57	
2:36 p.m.	150	210	20				
3:18 p.m.	150	200	20				
3:30 p.m.							Washed out cannula
4:15 p.m.	130	210	26	1445 c.cm.	675	57	
6:15 p.m.							Animal sacrificed by intravenous injection of 10 c.cm. of sodium pentobarbital

Pathological examination disclosed extensive loss of fluid at the site of injury. Gross examination of the viscera showed no striking evidence of generalized capillary injury but on microscopic examination the changes described in detail in the text were evident.

PENTOBARBITAL SODIUM ANESTHESIA AND THE PATHOLOGICAL CHANGES IN SHOCK

It may be argued that sodium pentobarbital is shock producing and that the reduction of the blood volume and the pathological changes encountered in these experiments are the result of using this agent as an anesthetic. There is no doubt that repeated and prolonged use of the barbiturates produces capillary damage (12). The fact that this agent was used as the anesthetic and that in the early stages of shock little or no evidence of generalized capillary injury was found strengthens our contention that the initial reduction of the blood volume is due principally to a loss of fluid at the site of injury. In the late stages of shock the use of sodium pentobarbital probably plays a rôle in the development of generalized capillary injury, and the degree of shock is probably more severe than would be encountered from the injury alone.

However, control experiments have shown that the anesthetic is not the principal factor in the production of either the pathological changes or the lowered blood volume. Four dogs were subjected to sodium pentobarbital anesthesia alone for periods of 4 to 16 hours. The physiological changes produced by this agent in a period of 7 hours are shown in Figure 13. Note that there is slight hemoconcentration and an increase in the total blood volume, but the plasma volume remains remarkably constant throughout the experimental period. The increase in the red cell volume is probably due to contraction of the spleen (10). Pathological examination of animals subjected to the anesthetic alone disclosed, in the early stages, that is, within 3 to 4 hours, comparatively little variation from the normal. There was moderate congestion of small and medium sized arteries and veins, and the intestines in two of the experiments had a somewhat dusky hue. The appearance of the bowel contrasted markedly with that seen following trauma. On microscopic examination there was found slight dilatation of vessels in the lungs, kidneys, and adrenals, and in the last mentioned a light infiltration of the zona reticularis with polymorphonuclear leucocytes. This was much less than that seen in the early stage of shock. In other words, the combination of the anesthetic and trauma

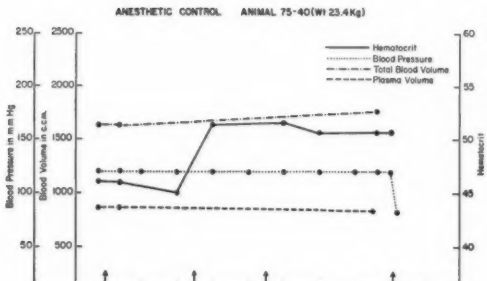

Fig. 13. The course of the changes in the hematocrit, blood pressure, plasma, and total blood volume following the administration of sodium pentobarbital—32 mgm. per kg. of body weight. There is hemoconcentration in keeping with the increase in the total blood volume but no reduction of the plasma volume. The increase in the red cell volume is due to contraction of the spleen.

produced more striking changes in the adrenal than was observed after the anesthetic alone. The gastro-intestinal tract and liver showed no variation from the normal. After longer administration of the sodium pentobarbital, 8 to 10 hours, the changes in the lungs, kidneys, and adrenals were more striking, but there was still no evidence of generalized capillary injury in the other viscera. With large doses over a sufficiently long period of time, the late changes of shock can be produced by the barbiturates as well as by a variety of other toxic agents (12).

It is concluded that under the conditions of these experiments the use of sodium pentobarbital as the anesthetic plays no significant rôle in the early and marked reduction of the blood volume; that the anesthetic alone is capable of producing pathological changes in the adrenals, lungs, and kidneys similar to those described, but that these changes are less marked than those observed when the anesthetic is followed by mechanical or thermal trauma; that the changes in the gastro-intestinal tract are not attributable to the anesthetic in the doses used as they were not observed in the control experiments; and finally that since it is a toxic agent and known to cause capillary damage, the administration of sodium pentobarbital probably accentuates the late pathological changes which have been observed in these experiments.

However, the use of sodium pentobarbital does not alter the principal contention of this study, namely, that in the early stages of traumatic shock there is comparatively little evidence of generalized capillary injury, whereas there is obvious and marked loss of fluid at the site of injury.

EVALUATION OF STUDY

Although it is generally accepted that a reduction of the effective blood volume is a constant finding in shock, the physiological and pathological mechanisms by which this is brought about are dependent largely upon the causative factors, and hence may differ widely. Shock may thus be regarded as the end-result of a variety of pathological and physiological processes. Thus, in anaphylactic shock, certain forms of poisoning, infection, and histamine intoxication, it is likely that the primary mechanism is generalized capillary injury. This not only increases the size of the vascular bed, thus bringing about a relative reduction of the effective blood volume, but eventually, as a consequence of loss of fluid and plasma throughout the viscera, produces an actual reduction of the blood volume with hemoconcentration. Histological studies in this form of shock reveal evidence of loss of fluid and cells throughout the viscera (12). On the other hand, in shock due to hemorrhage, the primary mechanism is a loss of whole blood from the circulation. There is a compensatory vasoconstriction. Postmortem examination discloses only generalized ischemia of the viscera. If death is not immediate, however, and the animal is kept in a state of shock by repeated small hemorrhages, eventually, as Blalock (4) has shown, there is evidence of generalized capillary injury and loss of fluids in the viscera. This generalized capillary injury may be the result of prolonged vasoconstriction with consequent ischemia of the viscera.

The present study indicates that in traumatic shock the early physiological and pathological mechanisms are similar to those in shock resulting from hemorrhage except that fluid and plasma are lost in higher proportion

than are red blood cells. This would seem to be the principal factor in initiating the reduction of the blood volume and the hemoconcentration. In the late stages of traumatic shock, either as a consequence of prolonged ischemia, adrenal insufficiency, the absorption of hypothetical toxins or factors not yet considered, there develops generalized capillary injury and loss of fluid throughout the viscera, particularly marked in the lungs, liver, kidneys, and gastro-intestinal tract. Thus, the final pathological picture is quite similar to that seen following poisoning, infection, anaphylactic shock, and other states in which capillary injury occurs.

If the late changes of traumatic shock are due solely to ischemia as a compensatory reaction to the reduced blood volume, it should be possible to prevent them by maintaining the blood volume at normal limits throughout the experimental period. This has been accomplished in a study of replacement therapy in experimental shock. The results will be reported in detail in a later publication (6). It can be briefly stated here, however, that plasma appears to be the most effective form of fluid replacement in traumatic shock, not only in restoring the blood volume to normal but also in ameliorating the late pathological changes of shock.

SUMMARY

Under the conditions of these experiments in which shock has been produced by thermal and mechanical trauma the principal factor in initiating the reduction of the blood volume is, as Blalock has long maintained, a loss of fluid at the site of injury. In late traumatic shock there is pathological evidence of generalized capillary injury and loss of fluid throughout the viscera. This appears to be a secondary rather than a primary phenomenon.

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THE McCLURE-ALDRICH TEST IN WATER BALANCE

DUGALD S. MacINTYRE, M.D., SVEND PEDERSEN, Ph.D., and
WALTER G. MADDOCK, M.D., F.A.C.S., Ann Arbor, Michigan

THE intradermal salt solution test was introduced in 1923 by McClure and Aldrich (1, 17) as "of value in determining the so called pre-edematous state of the tissues" in nephritis. It has been extensively studied since then in relation to edema (10, 11, 14, 20), fevers, (4, 5, 12), toxemia of pregnancy (15), thyrotoxicosis (9, 18), and jaundice (19). In 1927, Appel and Brill (2) first proposed its use in estimating the state of hydration of patients. Recently Hopps and Christopher (13) employed the test in following the postoperative water balance of 7 surgical patients, and stated that it was a sensitive and reliable index of the degree of hydration provided that the electrolyte balance had been taken into consideration. Our experience has not substantiated this opinion.

CONTROLLED DEHYDRATION STUDY

In the course of previous investigations in this laboratory on the water exchange of surgical patients, dehydration was produced in two normal individuals by limiting their water intake. Both subjects received an adequate maintenance diet of low water content, the mineral content was essentially constant. The full details of this experiment have been published previously (8) with the exception of the McClure-Aldrich tests which are reported at this time.

The technique which was used in performing the test was the same as described by the originators: 0.2 cubic centimeter of an 0.8 per cent saline solution was injected intradermally at the volar surface of a forearm and the anterior surface of a leg. Table I shows the water balance and McClure-Aldrich tests of subject J. N., Table II the same for subject R. M. Contrary to the expectations of Hopps and Christopher and others (16) who look for a more rapid disappearance of the wheal with dehydration, more time was needed for these two normal subjects to absorb the salt solution when dehydration was present than for the preliminary hydrated period. Furthermore, no consistent reduction in the disappearance time occurred in the recovery period.

STUDIES ON NORMAL INDIVIDUALS

White and Irvine-Jones have emphasized the variations in the disappearance time of the McClure-Aldrich test in normal individuals. In addition, Wohl and Ettelson reported that there were wide variations in fat individuals in different areas at the same time. Our subject J. N. also showed considerable differences between the disappearance times on the forearm and the leg. To learn more of these differences at first hand a series of the tests were run on 5 patients with local lesions but in good general health, who were taking a full general diet and as much water as they pleased. Table III shows the findings in these cases. It will be noted that wide variations occurred between the disappearance times in different individuals, between the different locations on the same subject, and between successive days in the same location on the same individuals. As much as a 40 minute variation was occasionally found between the tests.

STUDIES ON SICK SURGICAL PATIENTS

A series of carefully controlled studies of the water and electrolyte balance of sick surgical patients was next carried out in the hope that, in spite of the wide variations found in normals, the McClure-Aldrich test might show significant variations associated with changes in either the water balance or the plasma chemistry which would be of clinical value. A few of the most representative cases are herein reported.

Table IV shows the water balance, plasma chemistry studies and McClure-Aldrich tests on patient C. D., a 64 year old man with

From the Department of Surgery of the University of Michigan. Aided by a grant from the Horace H. Rackham School of Graduate Studies.

TABLE I.—WATER BALANCE DATA AND McCLURE-ALDRICH TEST FOR SUBJECT J. N.

Date 1935	Body weight gm.	Total available water intake gm.	Total water output gm.	Water balance gm.	Hematocrit Per cent	Blood specific gravity	McClure-Aldrich test, min.	
							Arm	Leg
Final 2 days of preliminary period Feb. 24	71373	2780	2406	+374	47.96	1.0575	63	68
Feb. 25	71378	2526	2536	−10	48.50	1.0598	58	65
Dehydration period Feb. 26	71728	688	1853	−1165	48.81	1.0601	58	70
Feb. 27	70585	625	1685	−1060	50.14	1.0623	75	61
Feb. 28	69588	641	1845	−1204	50.81	1.0631	96	84
Mar. 1	68393	1155	1779	−624	50.62	1.0652	66	114
	(Total negative water balance for 4 days 4053)							
Recovery period Mar. 2	67802	6917	2404	+4513	49.31	1.0604	62	95
Mar. 3	72244	2499	3256	−757	47.18	1.0603	80	96
Mar. 4	71355	3327	2931	+396	48.91	1.0619	105	119

pyloric obstruction due to gastric carcinoma. For 2 weeks previous to his admission there had been some vomiting and roentgen-ray examination showed a fair degree of pyloric obstruction. Clinically he showed signs of mild dehydration and loss of weight. In this case the test showed a shortened disappearance time with the mild dehydration and an increase toward normal as fluids were provided. This is precisely the finding one would expect if the test was a good indicator of the state of hydration, as suggested by Hopps and Christopher. However, this was not found to be a constant feature in any of the other cases examined.

Table V shows the data for patient C. B. who had a cholecystectomy and choledochostomy for a common duct stone with obstructive jaundice. Her postoperative course was essentially uneventful, the jaundice cleared completely and her general condition was good at the time the test was started on January 4, the nineteenth postoperative day. This patient was allowed to dehydrate for the

TABLE II.—WATER BALANCE DATA AND McCLURE-ALDRICH TEST FOR SUBJECT R. M.

Date	Body weight gm.	Total available water intake gm.	Total water output gm.	Water balance gm.	Plasma chlorides mg./100 c.cm.	CO_2 comb. power vol. %	Total plasma proteins gm./100 c.cm.	McClure-Aldrich test forearm min.
Preliminary period Mar. 17	59009	2097	2034	+63				60
Mar. 18	59076	2302	2300	+2	592		7.9	71
Dehydration period Mar. 19	59104	651	2081	−1430				95
Mar. 20	57705	651	1961	−1311				72
Mar. 21	56387	651	1307	−656	608	60.5	8.5	120
	(Total negative water balance for 3 days 3397)							
Recovery period Mar. 22	55764	3039	798	+2241				77
Mar. 23	58020	3464	2420	+1044				64
Mar. 24	59029	3211	3111	+100				87
Mar. 25	59126	2024	2269	−245				83
Mar. 26	58891				601	58.5	7.6	67

TABLE III.—McCLURE-ALDRICH TEST ON NORMAL PATIENTS

Patient	1		2		3		4		5	
	F. A. min.	S. H. min.	F. A. min.	S. H. min.	F. A. min.	S. H. min.	F. A. min.	S. H. min.	F. A. min.	S. H. min.
Jan. 18	42	75	40	75	30	39	27	82	25	34
Jan. 19	78	78	45	82	46	46	52	82	40	66
Jan. 20	39	82	42	96	29	45	95	95	23	40
Jan. 21	32	57	30	55	21	21	58	51	23	32
Jan. 22	40	79	48	77	32	39	38	87	30	45
Jan. 23	49	69	63	88	46	52	58	82	47	40
Jan. 24	30	60	35	59	38	38	55	66	38	60

F. A.—Forearm
S. H.—Shoulder

next 2 days by limiting the fluid intake to 500 cubic centimeters of water by mouth daily. After the January 5 period, when she had lost 2661 grams in weight, the average of the McClure-Aldrich tests showed a rise to 77 minutes from 66 minutes. On January 6 the weight decrease was 1339 grams and the McClure-Aldrich test dropped to an average of 45.5 minutes which according to Hopps and Christopher would be an indication of dehydration. On January 7, when replacement therapy was largely given intravenously, the McClure-Aldrich test approached the normal. On January 8 the patient was allowed to take only what she wished to eat and drink with the result that her intake was not adequate and she voided only 200 cubic centimeters of urine. At the end of this period the skin test showed a drop to an average of 42.2 minutes. The patient was again given an adequate in-

TABLE IV.—WATER BALANCE, PLASMA CHEMISTRY STUDIES AND McCLURE-ALDRICH TEST FOR PATIENT C. D.

Date 1939		12–28	12–29	12–30
Body weight	gm.	54080	53579	52919
Intake	c.cm.			
5% glucose I.V.		2950	2950	2928
Ringer's I.V.			1491	500
Output	c.cm.			
Wangensteen suction			2100	880
Urine			2150	2200
Specific gravity of urine			1.002	1.001
Total intake	c.cm.		4441	3428
Total sensible output	c.cm.		4250	3080
Plasma chlorides	mg./100 c.cm.	513	533	530
Carbon dioxide combining power	vol. %	47.8	45.5	45.3
Total plasma proteins	gm./100 c.cm.	6.97	6.40	6.43
NaCl in urine	gm.		0.761	0.440
McClure-Aldrich test	min.			
Right forearm		31	51	56
Left forearm		27	41	45
Right shoulder		56	59	70
Left shoulder		36	51	65
Average		38	50.5	59

TABLE V.—WATER BALANCE, PLASMA CHEMISTRY STUDIES AND McCLURE-ALDRICH TEST FOR PATIENT C. B.

24 hours ending		1940	1—4	1—5	1—6	1—7	1—8	1—9
Body weight		gm.	67601	64940	63601	65483	65303	66577
Intake		c.cm.						
Water by mouth				500	500	1150	1800	900
5% glucose	I.V.					2876		1946
Ringer's solution	I.V.					1500		2000
5% $NaHCO_3$	I.V.					250		
10% glucose	I.V.					400	200	
Output		c.cm.						
Bile				1330	820	950	500	1580
Blood				23	23	23	23	23
Urine				440	92	1320	200	1520
Specific gravity of urine				1.013	1.020	1.006	1.015	1.003
Total intake		c.cm.		500	500	6176	2000†	4846
Total sensible output		c.cm.		1793	935	2293	723	3123
Plasma chlorides		mg./100 c.cm.	609	587	566	550	567	573
Carbon dioxide combining power		vol. %	26.2	24.7	21.7	43.3	37.8	40.0
Total plasma proteins		gm./100 c.cm.	5.75	6.70	7.14	5.99	6.19	5.31
NaCl in urine		gm.		2.530	0.644	1.637	0.472	1.272
McClure-Aldrich test		min.						
Right forearm			?	43	29	49	30	23
Left forearm			62	88	36	52	30	32
Right shoulder			63	88	59	60	44	42
Left shoulder			77	88	58	67	65	65
Average			66	77	45.5	57	42.2	40.5

†Value incomplete because patient was on general diet which was not measured.

take intravenously to replace her fluid and electrolyte losses and at the end of this 24 hours she was well hydrated, her weight was within a kilogram of the original, but the average of the skin tests was only 40.5 minutes, which was 25 minutes less than the starting values. Summarizing this case there were discrepancies in the relationship between the degree of hydration and the McClure-Aldrich test which seemed to make the latter unreliable.

Table VI shows the data for a 63 year old male with pyonephrosis and uremia. On admission he was comatose and showed signs of marked dehydration and acidosis. The general examination was otherwise essentially negative except for the urine which was found to be loaded with red and white blood cells and a mixed bacillary and coccal infection. An examination of Table VI shows that the situation is a complicated one, the carbon-dioxide combining power remained below normal throughout the study, the plasma chlorides decreased in the 4 days from 521 to 431 milligrams per cent, considerable sodium chloride was excreted in the urine daily, the urine output was high, yet on January 7 there was a gain of 2.3 kilograms which, since his calorific intake was insufficient, must have been due to water and salt retention. In spite of all these variations the McClure-Aldrich test on January 5, the beginning of the study, was not much different from that on January 8, the end of the study, and one can deduce little from it in relation to the rest of the findings.

The next case, Table VII, is that of a 33 year old female who on admission was mark-

TABLE VI.—WATER BALANCE, PLASMA CHEMISTRY STUDIES AND McCLURE-ALDRICH TEST FOR PATIENT G. B.

24 hours ending	1939	12—5	12—6	12—7	12—8	12—9
Body weight	gm.	65392	66595	67641	67453	66805
Intake						
5% glucose I.V.	c.cm.	†(3000)	700	3930	5900	1000
1% $NaHCO_3$ I.V.			2506			
5% $NaHCO_3$ I.V.			200	250	250	
Ringer's solution I.V.				1480		4290
Normal saline I.V.						500
Blood I.V.						300
Output	c.cm.					
Emesis			150	240	165	
Blood			75	75	25	20
Urine			1610	4535	5250	5815
Specific gravity of urine	c.cm.		1.007	1.004	1.005	1.003
Total intake	c.cm.		3406	5660	6150	6090
Total sensible output	c.cm.		1832	4850	5440	5835
Plasma chlorides	mg./100 c.cm.	521	487	485	431	551
Carbon dioxide combining power	vol. %	23	34.3	35	39.7	38.4
Non-protein nitrogen	mg./100 c.cm.	166.5		172	131.8	108
Total plasma proteins	gm./100 c.cm.		6.4	6.19		5.89
NaCl in urine	gm.		3.317	9.108	9.679	10.752
McClure-Aldrich test	min.					
Right forearm		68	—	—	10	
Left forearm		—	60	60	—	
Right shoulder		80	90	65	85	
Left shoulder		80	95	80	80	
Abdomen		80	90	75	90	
Average		77	84	72	66	

†Given before test started.

edly dehydrated. Although the history was unreliable it was felt that the patient most probably had had ergot poisoning due to drug therapy 9 months previous to admission. A left midthigh amputation for gangrene of the left leg had been done, and on admission there was gangrene of the right great toe and of the right middle finger. No wrist pulsations could be felt, but her circulation showed no evidence of impairment above the elbows. With the hydration of the first 24 hours the patient gained 3.7 kilograms, and the plasma chlorides increased approximately 100 milligrams per cent to reach a level close to normal. The urine output was good and sodium chloride was excreted by the kidneys. In spite of this, the time for the McClure-Aldrich tests was far below normal before treatment was given and remained so after hydration. Cohen and his co-workers (6, 7, 21) showed that there was more rapid absorption of the intradermal salt wheal in areas with disturbed peripheral circulation and this condition may have been present on the forearms but there was no indication of disturbed circulation in the shoulder region where far below normal readings persisted. There was no apparent significance of the McClure-Aldrich test in relation to the water and electrolyte balance of this patient.

SUMMARY

Although Appel, working with Brill in 1927 (2), first advocated the use of the McClure-Aldrich test as an index of water metabolism,

TABLE VII.—WATER BALANCE, PLASMA CHEMISTRY STUDIES AND McCLURE-ALDRICH TEST FOR PATIENT B. C.

24 hours ending		1940	1—22	1—23	1—24	1—25
Body weight		gm.	36096	39801	41308	41285
Intake Water orally		c.cm.		627	344	499
5% glucose	I.V.			2305	945	1000
10% glucose	I.V.				2000	2000
Ringer's solution	I.V.			3961	570	640
Blood	I.V.					500
Normal saline	I.V.					368
Output Urine		c.cm.		2585	1890	3840
Specific gravity of urine				1.009	1.011	1.010
Total intake		c.cm.		6893	3859	5007
Total sensible output		c.cm.		2585	1890	3840
Plasma chlorides		mg./100 c.cm.	429	531	498	
Carbon dioxide combining power		vol. %	50.3	45.9	43.0	
NaCl in urine		gm.		2.559	2.060	4.800
McClure-Aldrich test Right forearm		min.	13	6	5	5
Left forearm		min.	13	6	17	3
Right shoulder		min.	18	19	26	17
Left shoulder		min.	18	21	26	22
Average of shoulders		min.	18	20	26	19.5

he later discontinued its use in 1928, because, working with Farr (3), he found no correlation between it and other indices of water metabolism, especially with the blood specific gravity. In only 1 of the 4 presented cases of dehydration or disturbances of the electrolyte balance in sick patients have we been able to show any correlation between the McClure-Aldrich test and the state of hydration or the changes in the blood chemistry. In a closely controlled experiment there was no relation between the disappearance time of the wheal and severe dehydration brought about by limiting the water intake of two normal subjects. Further, we have confirmed the findings of others that there are marked variations in the test when it is carried out on normal individuals.

CONCLUSION

The McClure-Aldrich test was not found to be a sensitive or a reliable index of the state of hydration of experimental subjects or surgical patients.

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THE VENOUS CIRCULATION IN THE LOWER EXTREMITIES DURING PREGNANCY

J. ROSS VEAL, M.D., F.A.C.S., and HUGH HUDSON HUSSEY, M.D.,
Washington, District of Columbia

LOCAL disturbances in the venous circulation of the lower extremities are quite common both during and immediately following pregnancy. Such disturbances are manifested by the development of varicose veins or the aggravation of varicosities already present; by the appearance of edema in which cardiac, renal, nutritional, or endocrine causes are obviously lacking; and by the occurrence of acute thrombophlebitis, usually as a postpartum complication.

That the state of being pregnant is influential in the production of edema and varicose veins in the lower extremities is generally recognized. The mechanism responsible for these symptoms, however, has never been clearly demonstrated. The symptoms are entirely absent in many patients, are mild in others, and are severe in still others. That some anatomical or physiological factor or "peculiar predisposition" exists in some pregnant women but not in others is suggested by the variability of time of onset, extent, and course of the edema and varicose veins. Since such manifestations are common complications of pregnancy in all races and all classes it does not seem logical to assume the existence of any "peculiar predisposition," such as congenital weakness of the valves of the venous system.

Certain physiological changes occur during pregnancy that might alter the venous circulation in the lower extremities. It is generally accepted that there is an increase in the total blood volume. There is also an increase locally in the volume of blood in the pelvic veins. This is due partly to the augmented vascular supply incident to growth of the uterus and partly to the formation of arteriovenous communications in the placenta. These physiological changes are found in every pregnancy and consequently do not explain the variability of occurrence of varicose veins and edema. Furthermore, such changes are hardly of sufficient magnitude to account for these symptoms in any case.

Changes in the anatomy of the pelvic organs during pregnancy produce considerable obstruction to the venous return from the lower extremities. Furthermore, the anatomical changes are variable. The position and size of the uterus, the length and mobility of the supporting ligaments, the size of the pelvis, and the tone and development of the abdominal muscles, all may vary to some degree in different pregnant women. Such anatomical variations may account for differences in the degree of obstruction to the outflow of blood from the lower extremities. In some women the obstruction may be sufficient to produce varicose veins and edema.

If obstruction of the femoro-iliac veins is the principal factor in the pathogenesis of edema and varicose veins in pregnant women, it is logical that the most direct approach to the early detection of these disturbances might be by measurements of the blood pressures in the veins of the lower extremities. It seems probable also that such measurements might yield a more complete explanation for the clinical inconsistency of varicose veins and edema in pregnant women. Burwell has demonstrated that the pressures in the femoral veins recorded with the patients in the supine position increase progressively during pregnancy, without any significant change in the venous pressures in the upper extremities, and that delivery is followed by prompt restoration of the pressures to normal. We have confirmed these findings. However, the height of the femoral venous pressure recorded with the patient lying down cannot be correlated

From the Surgical Service, Gallinger Municipal Hospital, and the Department of Medicine, Georgetown University School of Medicine, Washington, D. C.

with the occurrence of varicose veins and edema. Thus patients with marked edema and varicose veins may have lower femoral pressures recorded in this way than some patients who have neither of these symptoms, so that confirmation of venous obstruction as the cause of the symptoms is not obtained.

As far as we have been able to discover from reviewing the literature, no attempt has previously been made to measure the pressures in the deep veins of the lower extremities of pregnant women with the patients standing. It must be recognized that such a procedure might elicit evidence of venous obstruction that would be lacking in venous pressure measurements obtained in the usual way. This presumption is based upon the fact that the upright posture apparently aggravates the manifestations of obstruction of the veins in susceptible patients. Furthermore, in patients with edema, rest in bed usually relieves the edema, and if varicose veins are present these promptly collapse. For measurement of venous pressures in the lower extremities with patients standing, deep veins must be used for accurate results. The pressures in the superficial veins are much too readily influenced by local factors, such as muscular exercise and tone, the state of the veins and the venous valves, etc. For reasons that will be obvious later, the popliteal vein is most suitable for the purpose in view.

Unfortunately, a single measurement of the pressure in the popliteal vein with the patient standing is impossible of interpretation by ordinary means. Only the local pressure (pressure at the level at which the vein is punctured) can be estimated. The reference point for the zero level of the manometer for measurement of the pressure in terms which take into account the hydrostatic pressure is unknown. Even in the absence of localized venous obstruction, the local popliteal pressure shows a great and as yet unaccountable variation in different patients. Repeated measurements of the local pressure in the popliteal vein in a pregnant woman might be useful for demonstrating progression of venous obstruction, but even this is doubtful. It has been our experience in previous studies (3, 4) that there is no constant relationship between venous obstruction and the height of the venous pressure measured in the usual way. This is due to the fact that obstruction of the peripheral veins leads to the development of collateral channels which often are adequate to carry away the blood under resting conditions, so that the venous pressure may remain relatively normal. In such cases, however, exercise imposes conditions in which the venous collateral circulation may be quite inadequate. For example, exercise of an extremity in which the veins are partially obstructed may augment the inflow of arterial blood many times what it is during rest. Then the venous pressure in the affected extremity will rise to a varying degree, depending on the amount of venous obstruction and the extent of the collateral circulation, although it may have been within the normal range before exercise began. These facts led us to devise means for measuring the venous blood pressure during standard "exercise tests" in patients suspected of having obstruction of the veins of the upper or lower extremity.

The "exercise test" of venous pressure in the lower extremity entails the use of the popliteal vein. The apparatus (Fig. 1) for measurement of popliteal venous pressure consists of a mercury U-tube manometer, one arm of which is straight, the other arm bent at an angle to facilitate attachment of a piece of rubber tubing. A millimeter scale is affixed beside the straight arm for purposes of recording pressures. Measurements obtained on this scale of course must be doubled in order to represent true records of pressures in terms of millimeters of mercury. The other arm is filled completely from the surface of the column of mercury to its tip with 2.5 per cent sodium citrate solution. The height of the column of mercury beside the millimeter scale is noted. Next a sterile length of rubber catheter tubing having a needle adaptor in one end is filled completely by means of a sterile 5 cubic centimeter syringe with sterile 2.5 per cent sodium citrate solution. This tubing is clamped with a small hemostat and its free end is then slipped on the designated arm of the manometer, care being taken to exclude air bubbles from the system. The manometer is adjusted on its supporting stand

so that the zero level of the column of mercury is on a plane with the point at which the venipuncture is to be made. This adjustment is accomplished by means of a carpenter's level. The patient is instructed in the procedure of the test and is shown how to perform the exercise. She stands erect, with feet slightly apart, on a smooth table set against the wall, where supports are provided for her hands. The lower half of the thighs and the legs are exposed, shoes and stockings being removed. Standing behind the patient, the operator palpates the lower border of the patella with his index finger, and locates with the thumb of the same hand a point on this same level and just medial to the lateral head of the gastrocnemius and the plantaris muscles. After appropriate sterilization of the skin, a wheal is produced at this point with 1 per cent solution of novocain. A 19 gauge, 1½ inch needle, attached to a 5 cubic centimeter syringe is inserted through the anesthetized area and is pushed straight forward until the popliteal vein is punctured. During the insertion of the needle, traction is exerted upon the plunger of the syringe so that entrance of the needle into the vein can be instantly recognized by the spurt of dark red blood into the syringe. The depth to which the needle must be inserted varies somewhat in different individuals but usually is about 2.5 centimeters. The patient is warned that she may experience a shock of pain radiating down her leg. She is cautioned not to move this leg but to inform the operator of the discomfort. This happens not infrequently and is caused by pricking the tibial nerve which lies close to the lateral surface of the vein. The pain is only momentary and guides the operator for reinsertion of the needle slightly more medially. When the popliteal vein has been entered the syringe is detached from the needle, and the adaptor of the venous pressure apparatus is connected to the needle. Loss of a small amount of blood is unavoidable during this transfer. Finally, the clamp is removed from the tubing of the apparatus.

The column of mercury in the manometer will quickly come to a level which indicates the local blood pressure in the vein. The height of this level is recorded as the initial

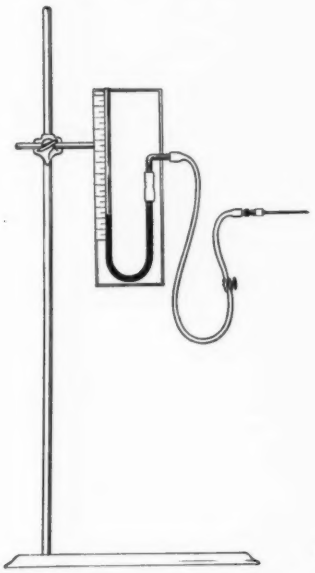

Fig. 1. Mercury U-tube for measurement of popliteal venous pressure. Connection to popliteal vein through closed system.

venous pressure. The patient then begins the exercise which consists in rising on her toes repeatedly (20 to 30 times) for 1 minute. It is important that she use the wall supports for her hands only for the purpose of steadying herself and not as a means of assisting the exertion, that she breathe regularly during the exercise, and that she relax the muscles of her legs each time her heels are lowered to the surface of the table. During the test it is necessary for the operator to support the rubber tubing of the apparatus with his hand in order to keep the needle horizontal and prevent it from slipping. The changes in venous pressure during exercise are recorded, and the pressure is observed for a short time after exercise has ceased. The needle is then withdrawn and firm pressure is applied for about a minute at the site of venipuncture. The patient is required to walk around the room for a few minutes at the conclusion of the test in order to prevent venous thrombosis.

In normal individuals and in patients with edema of the lower extremities due to nephrosis, nutritional deficiency, or lymphatic ob-

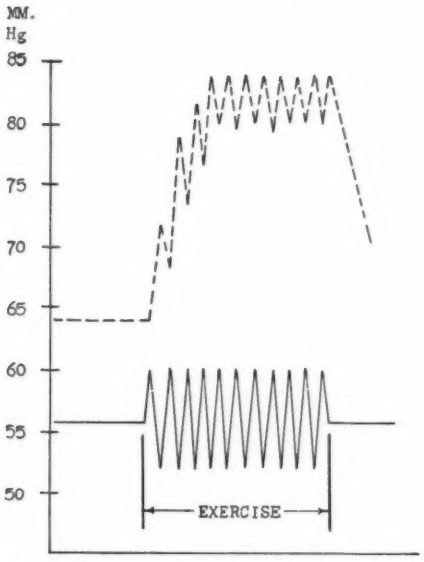

Fig. 2. Popliteal venous pressures in case of right femoro-iliac thrombosis. Demonstrates contrast of obstructed and nonobstructed legs. —, left leg; ————, right leg.

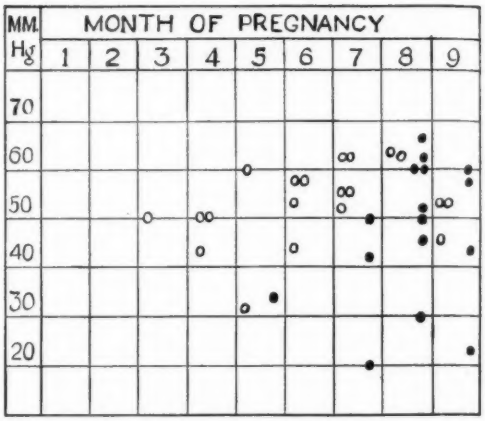

Fig. 3. Initial popliteal venous pressures in 36 pregnant women. Note absence of correlation between height of venous pressure and edema or varicose veins. ○, Patients with edema or varicose veins; ●, patients with edema and/or varicose veins.

struction, the popliteal venous pressure is little affected by the exercise described. The column of mercury in the manometer fluctuates usually above and below its initial level through a distance of 8 to 12 millimeters but shows no tendency to rise progressively. On the other hand, in patients having significant obstruction of the femoral or iliac veins due to thrombosis, compression by tumor, or other cause, the popliteal venous pressure, in addition to oscillating with each movement of the patient as she performs the prescribed exercise, tends to rise progressively. The amount of rise theoretically should depend mainly upon the degree to which there is delay in the outflow of blood through the obstructed veins. However, it has been our experience that the pattern which can be traced from the response of the venous pressure to the exercise imposed is of more practical importance than the amount of rise. In other words, a pattern which shows only oscillation of the pressure above or below the initial venous pressure indicates that the venous system is adequate under conditions of the test; while a pattern which shows a progressive rise of the pressure to any degree, in addition to the same type of oscillation, indicates that the venous system is inadequate. Figure 2 presents the contrast of the two types of pattern. In this case of femoro-iliac thrombosis of the right side the popliteal venous pressures clearly demonstrate the presence of venous obstruction in the right leg and the absence of obstruction in the left leg.

It was our interest in the preparation of this present report to apply the procedure of measurement of popliteal venous pressure with the patient standing and during exercise to pregnant women as a part of the search for an explanation of the cause of varicose veins and edema.

CLINICAL RESULTS

Thirty-six pregnant women were studied in the order of their admission to the prenatal clinic in the outpatient department at the Gallinger Municipal Hospital. No attempt at case selection was made, but no patient in the group had any detectable toxemia or other complicating illness. All of the patients were of the negro race. Twenty of the 36, or 56 per cent, had neither edema nor varicose veins,

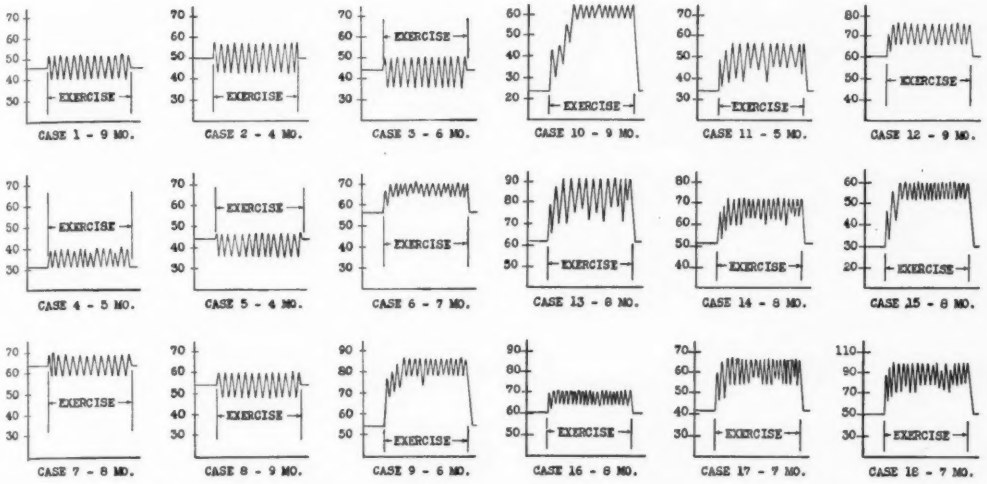

Fig. 4. Popliteal venous pressures (mm. of mercury) in pregnant women having no edema or varicose veins. Note the uniformity of patterns except in Cases 6 and 9.

Fig. 5. Popliteal venous pressures (mm. of mercury) in pregnant women having edema and/or varicose veins. Note uniformity of patterns.

while the 16 others, or 44 per cent, had edema, or varicose veins, or both. Fourteen of the women, 39 per cent, were primiparas, and 22, 61 per cent, were multiparas. Only 4 of the 14 primiparas, 29 per cent, had edema or varicose veins or both, while 12 of the 22 multipara, 55 per cent, had these manifestations. Although the group is small, this higher incidence of such manifestations in multiparas is in keeping with the general experience of obstetric practice.

Because of the social level of the patients attending the clinic at which our studies were made, comparatively few patients were observed early in pregnancy (Fig. 3). Thus only 1 of the 36 patients was in the first trimester, 10 were in the second trimester, and the 25 remaining were in the final trimester. The single case observed during the first trimester had neither edema nor varicose veins, but 15 of the 25 in the third trimester, 60 per cent, had edema and/or varicose veins. The higher incidence of these manifestations in the latter months of pregnancy again is in accord with usual obstetric experience.

In each case a recording of the initial pressure in the popliteal vein was obtained with the patient standing quiet, after which the "exercise test" as herein described was performed. There was no immediate correlation between the initial pressures and the presence of edema or varicose veins (Fig. 3). In fact, the 3 lowest initial pressures were recorded in patients with edema and varicose veins. Of the 20 patients having neither edema nor varicose veins, 18, or 90 per cent, showed normal patterns of the popliteal venous pressure during exercise. That is, the pressure fluctuated above and below the initial pressure or oscillated between the initial pressure and a reading not more than 8 millimeters of mercury above the initial pressure. Figure 4 demonstrates examples of the normal patterns obtained in these cases, except Cases 6 and 9. In these 2 cases, 10 per cent, the response of the popliteal venous pressure to exercise followed an obstructive pattern. In Case 6, after an initial reading of 56 millimeters, the venous pressure fluctuated during exercise from 64 to 70 millimeters. In Case 7, the initial reading was 54 millimeters; during exercise the pressure ranged from 68 to 86 millimeters.

In the 16 patients having edema or varicose veins or both, obstructive patterns of response of the popliteal venous pressure during exer-

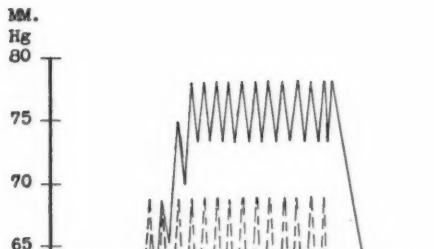

Fig. 6. Popliteal venous pressures in pregnant woman having edema of the left leg only. Note normal pattern in nonedematous leg and obstructive pattern in edematous leg.—, left leg; ————, right leg.

cise were obtained in all cases. Figure 5 gives some examples of these patterns. In 2 of these cases (Cases 12 and 16), the fluctuations of pressure during exercise were of relatively low order, possibly indicating that the venous obstruction was of milder degree. In the 14 remaining patients, patterns typical of severe venous obstruction were obtained during exercise. For example, in Case 10 the fluctuations of pressure reached peaks of 40 millimeters of mercury higher than the initial pressure of 24 millimeters; in Case 15 the oscillations were 22 to 30 millimeters and in Case 18, 20 to 40 millimeters higher than the initial pressure. In one other case not shown in the figure the peaks of the oscillations were 56 millimeters higher than the initial popliteal venous pressure.

EVALUATION

The assumption that postural dependent edema and varicose veins in pregnant women are due mainly to compression of the iliac veins by the enlarging uterus or as the result of other anatomical changes, has always had some clinical substantiation. However, it has been difficult to reconcile with this assumption the fact that all pregnant women do not develop these manifestations. Venous pressures measured in the usual manner in the femoral veins with the patients supine do not differ significantly in the group of women with supposed evidence of venous obstruction and the group without such clinical evidence. Although the complete reconciliation of these facts has not been achieved, the original assumption has been sustained by the patterns obtained by the measurement of the pressures in the popliteal veins during exercise. In addition it has been learned that in pregnant women who show varicose veins or edema of the type under discussion there actually is a more severe degree of venous obstruction than in women who are free of these symptoms. Failure of femoral venous pressure determinations of the usual type to demonstrate this difference must be ascribed to the incompleteness of the procedure. It does not take into account the facts that a venous system may be adequate during rest and grossly inadequate under conditions of ordinary activity and that an upright posture may play a large part in aggravating obstruction of the venous flow from the lower extremities.

Further clinical proof of the obstructive origin of edema and varicose veins during pregnancy is found in the occasional case in which the symptoms are strictly unilateral. For example, in one patient of the group studied there was moderate edema of the left lower extremity without edema of the right at the eighth month of pregnancy. This kind of phenomenon would be difficult to explain except as the result of obstruction of the left iliac vein, and indeed the patterns obtained on measurement of the popliteal venous pressures during exercise (Fig. 6) support the clinical evidence. The pattern from the left popliteal vein is one of venous obstruction, while that from the right popliteal vein is normal. This case and the type of case in which edema or varicose veins are most prominent during the early months of pregnancy and tend to regress as pregnancy continues strongly suggest that the position of the uterus may be important in the pathogenesis of localized obstruction of the deep veins. However, speculation as to the anatomical or other factors responsible for heightening the degree of occlusion of the veins in pregnant women who develop the

symptoms discussed here cannot be very fruitful in the absence of additional careful studies of the anatomy and physiology of the venous system.

In our opinion, measurements of the popliteal venous pressures during exercise in pregnant women who show edema of the lower extremities yields information which is essential to the care of the patient. If the venous pressure pattern is not of the type found in cases of venous obstruction, some other cause for the edema should be sought. On the other hand, if an obstructive pattern is obtained, care of the patient should be directed to the prevention of varicose veins. One of us (2) has shown that protection of the superficial veins by means of elastic stockings will prevent or greatly minimize the development of varicose veins in patients having localized obstruction of the femoro-iliac veins. The stockings are even more useful in pregnant women than in some other cases because the duration of venous obstruction is relatively so much shorter. If the superficial veins are protected in this way, their valves remain intact and varicose veins are consequently less likely to appear.

SUMMARY AND CONCLUSION

1. The assumption that postural dependent edema and varicose veins of the lower extremities in pregnant women are due to localized obstruction of the deep veins is supported by the types of pressure curve obtained when popliteal venous pressures are recorded during exercise.

2. The factors responsible for increasing the degree of localized venous obstruction in some pregnant women to the point of causing edema or varicose veins or both are not perfectly understood. The size and position of the uterus are factors of recognized importance.

3. In pregnant women manifesting significant obstruction of the femoro-iliac veins, provision of adequate support for the superficial veins by means of elastic stockings minimizes or prevents the development of varicose veins.

We wish to thank the members of the Department of Obstetrics of the Gallinger Municipal Hospital for their co-operation in these studies.

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PERSISTENCE OF FUNCTION OF SKIN GRAFTS THROUGH LONG PERIODS OF GROWTH

JAMES BARRETT BROWN, M.D., F.A.C.S., and FRANK McDOWELL, M.D.,
St. Louis, Missouri

FUNCTION has been found to persist in large skin grafts that have been in place during long periods of growth and the fundamentals that have proved of value in carrying out large surface repairs are reviewed here.

Both thick split and full thickness grafts do seem to grow, or at least stretch out, with growth of the body area and to permit normal movement, if they have been successful from the start. This has been true in many patients and over areas of the body from the face to the feet (Figs. 1 to 10).

There is a condition that may be called *generalized skin shortening* of an area in which there is no evident distortion but a definite lack of flexibility and ease of function. This may result from failure of releasing the scar sufficiently or from growth of the area without enough enlargement of original grafts. The condition may be likened to clothes that are too tight or it may be said that the skin envelope is too small. This means that *scar and its contracture persist until released;* if it is completely released early in life, the repair should last; if, with increased growth, the shortening does appear, then more skin can be let in by simply opening the tightest area, allowing the edges to retract and filling the resultant defect with suitable grafts. Where the scar tissue is very thick, however, the edges will not retract when opened and then large areas have to be excised down to good soft tissue and still larger grafts applied (Figs. 6 and 10).

By *satisfactory late function of the grafts* is meant: (1) enough skin for free movement; (2) moderate looseness; (3) ability to withstand the usual trauma of getting around; (4) the development of normal sensation. Full normal sensation usually develops in free skin grafts and is influenced by the amount of deep scar that is left and, of course, is dependent on there being sensory nerves in the area.

From the Department of Surgery, Washington University School of Medicine, St. Louis, Missouri.

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Fig. 1. Extreme deformity of neck and jaw corrected in 2 thick split graft and 1 full thickness graft operations. Recorded after an 8 year period of growth with complete restoration of contour. Surface smoothness can be improved with further grafts when patient wishes. Both axillae also repaired.

Metaplasia of grafts (and flaps also) does not take place and, therefore, a really normal sole of the foot, for instance, cannot be restored. This area is specialized to the point of being an organ; the skin and subcutaneous tissues are different from birth and the peculiar bearing qualities are not developmental. A graft or a flap on a sole may make calluses (or even annoying warts) but it will not metaplase into true skin or subcutaneous tissue of the area. They always have to be protected and the wart formation guarded against (Figs. 4 and 9). If hair is transplanted, it will continue to grow, except that it may be worn off.

Skin grafts transplanted to normal mucous membrane surfaces, such as the mouth, larynx, and eye socket, show no evidence of a change to a mucous membrane. The skin simply persists as such and even raises hair in these areas if there are any functioning follicles in the graft.

The results of grafting vary in different regions and with the type of lesion. A graft put on a soft base with a good blood supply can be expected to be more certain than if put over the shin or ankle where there is little deep pad to help absorb shocks and trauma. Likewise, an old x-ray burn or leg ulcer with deep and surrounding fibrosis and lack of resiliency of the tissues cannot afford as good a bed or area for a graft as a simple burn. Old chronic leg ulcers with deep scarring and edema tend to recur, so that improvement of local circulation is necessary if the repair is to prove efficient; the graft itself, of course, may assist in this.

Fig. 2. Difficult contracture of mouth and neck, repaired with three thick split grafts from clavicle to level of nose. Contour has remained satisfactory after 13 year growth period.

Fig. 3. Marked distortion and jaw twisted down into open bite; corrected in 2 split graft and 2 full thickness operations. Normal profile and occlusion of teeth resulting and recorded a second time after 10 year period of growth.

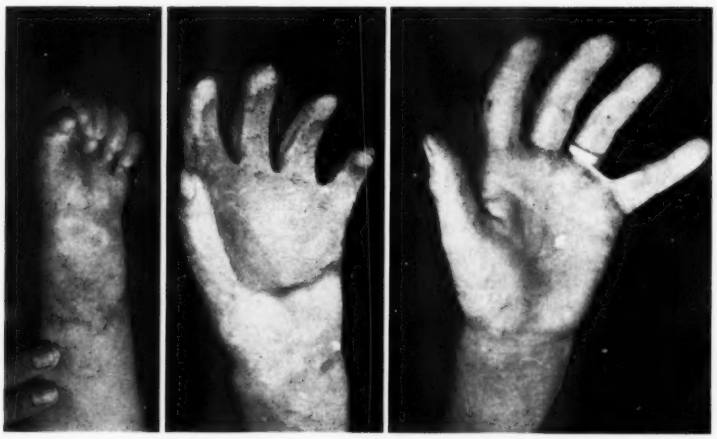

Fig. 4. Replacement in 1 operation with a full thickness graft of entire palmar surface of hand and fingers. The graft has definitely enlarged and is satisfactory to the boy in every way after 12 years of growth, following first recording.

A frequent cause of loss of grafts applied for long-standing fibrosed ulcers is failure to remove the scar down to soft tissue; one should avoid denuding bone or tendons in the process, however.

Although grafts and flaps are not being compared, a successful graft may be more apt to continue satisfactorily throughout a growing period than a pedicle flap, because flaps have a tendency to hump up and become heavy from fat rather than to spread out.

Cosmetic results with free skin grafts may not be as good as the functional results de-

Fig. 5. One of the most difficult types with heavy distorting scar encasing entire arm and wrist. Required 5 split grafts but complete function of the skin grafts persists after a 5 year period of growth.

scribed. What would be a good functional result on a leg or axilla would be a very poor one on the face, because of roughness and pigmentation. However, the same general rule applies for a late, desirable cosmetic result as for function: if the graft has been satisfactory soon after operation, it will probably persist as such. The unevenness and wrinkling can be minimized by careful dissection of the base and by using full thickness rather than split grafts. However, chances of too much pigmentation persist without relief at the present time, and the patients may have to rely on the application of cosmetics (Figs. 1, 2, 3).

By studying these patients several years after operation, the fundamentals of treat-

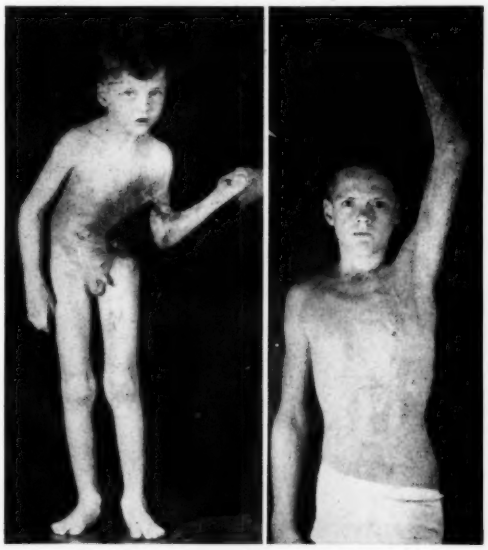

Fig. 6. Very deep, widespread burn. Patient tided over critical period with large, split homografts from mother. Axilla then released in 2 split graft operations. Generalized skin shortening across abdomen and flank released 2 years later with split grafts. Normal function recorded a second time, 9 years after operation. Grafted area extends from iliac crest all the way up through axilla and down over arm.

Fig. 7a

b c d

Fig. 7. a, b, c, Complete circular loss repaired in 3 split graft operations. Shown after 2 years. d, Same type of burn 8 years after 1 single operation.

Fig. 8. Complete function from 2 split graft operations. No foot drop even though nerve was exposed in dissection. Patient came in for amputation. Recorded a second time after 9 year growth period.

ment for early lesions have been made more clear and may be briefly outlined.

Repairs of large surface defects if possible should be made early, before debilitation, scarring, and contracture have taken place. Most burns can be made clean enough to graft in 3 or 4 weeks, but, if good care is not given the areas, infection, pain, and debilitation develop, and late deaths may occur (Fig. 7).

Homografts may be used for temporary relief during waiting periods, but these grafts never persist in spite of attention to blood grouping down into the "m" and "n" subgroups. What does happen is usually a "take" of the grafts with a period of respite from the painful dressings for several days or weeks. With this, there is a general improvement, a clearing up of infection and, because of these things, a stimulation to spontaneous epithelization. Therefore, actual healing may occur even though the homografts are completely absorbed and this process may be so marked that some observers may think the homografts themselves have persisted (Fig. 6).

Pinch grafts or small deep grafts are used occasionally in areas that are covered by clothes and have the advantage of not requiring a major operation. However, they are unsightly in any area and may be replaced later with larger grafts if desirable.

When large areas are to be dealt with consistently, it is advisable to develop a *simple, direct method of cleaning wounds, obtaining large sheets of grafts* of suitable thickness, and applying them accurately to insure growth. *The donor site* of these grafts is most important and, when large areas are denuded, it is necessary to split through the skin to leave some deep gland elements to dedifferentiate into squamous epithelium so that a new surface may form. With careful dressing of the donor site, surface healing will be satisfactory in 12 days. As many as four crops have been taken from the same area and one crop taken 19 days after the previous one. If the reverse is true, that is, if the skin is cut through or the donor site becomes infected, healing will be delayed for weeks and no subsequent crops can be taken. This is somewhat comparable to the loss of epithelial healing that occurs under an infected tannic acid or silver nitrate crust (Fig. 8).

Fig. 9. Restoration in 1 split graft preceded by bone correction by Dr. Crego. Function satisfactory with graft on sole of foot after 9 years of growth. Free grafts can work on the foot only if sufficient deep pad has been left; otherwise, a thick pedicle-flap is used.

Any method that leaves behind enough skin for healing, splits through the skin, and for this reason the term *"thick split graft"* has been used. Many other names have been suggested but the term "thick split" seems most descriptive. The usual thickness is from one-half to three-fourths of the skin and the thickness can be graduated in cutting with some practice. The thickness of the graft varies in relation to the full thickness of the skin which, itself, varies greatly according to age, nutrition, race, and its position in the body. The actual measurement of the thickness of the graft has to be in relation to these variables. The main essentials are a long, sharp knife and some means of creating a diaphragm of the skin on which to cut.

Saving a good donor site on badly burned patients is important for obtaining smooth full thickness grafts when the final operations are to be done about the face and neck. Usually an entire thigh or the lower abdomen can be left for this work, but it is frequently found that pinch grafts have been removed right out of the center of these areas.

Fig. 10. Generalized skin shortening of 26 years' duration that prevented sitting down normally. Relieved with thick split skin grafts and shown after 15 years' duration of function.

With these criteria fulfilled, *huge areas may be grafted.* Up to 600 square inches have been done in one patient and 100 to 200 square inches at a time are possible. To do this, huge grafts are necessary and they have been taken as large as 36 inches by 4 inches. To try to repair large areas with small chips of grafts is uncertain and nerve-racking. Even at best, long operative times are necessary and the condition of the patient must be watched closely.

However, when large areas are grafted at one sitting, the *total* amount of work which must be carried out is greatly lessened (Figs. 7 and 8).

It seems definite that large surface repairs can be done successfully with free grafts without resorting to the cumbersome use of flaps in most instances. Growth (or stretching) of the grafts occurs so that, even after the patient has passed through long periods of growth, the restorations are found to be satisfactory.

THE EFFECT OF PARTIAL OBSTRUCTION OF THE COMMON BILE DUCT

NORMAN W. THIESSEN, M.D., and RAMON F. HANZAL, Ph.D., Cleveland, Ohio

PARTIAL or recurring obstruction to the common bile duct in man causes many distressing symptoms. In the absence of stone, stricture, or cancer, these symptoms have been attributed variously to dysfunction of the gall bladder, tonic or structural disturbances of the sphincter of Oddi, and inflammation of the pancreas. The differential diagnosis of these conditions, when jaundice is not present, is difficult. Any diagnostic help, therefore, would be a distinct assistance. An attempt was made experimentally to produce a similar condition in the dog by causing a partial obstruction to the common bile duct and to observe the effects.

The first clinical report of "gall-bladder colic" without stone or infection was made by Krukenberg in 1903. Aschoff and Bacmeister (3) in 1909 described what they called the "stasis gall bladder," distinguishing the hypertrophic and atrophic types, depending on the condition of the muscle layer of the gall bladder. In 1920 Schmieden (38) correlated the pathological with the clinical findings and stressed mechanical hindrances to the flow of bile as the cause of the symptoms. Berg in 1922 found a hypertrophy of the sphincter of Oddi and suggested a functional disorder of this muscle as the cause for biliary stasis. This observation has been confirmed since then by Westphal (48), Nuboer, Newman, Giordano and Mann (15). This theory already had been suggested on physiological grounds by Oddi and by Meltzer. Westphal (49) then classified these states as atonic and hyperkinetic with a further differentiation of the hyperkinetic type into hypermotile and hypertonic states. More recently several observers have demonstrated a physiological obstruction to the lower end of the common bile duct in man (McGowan, Butsch, and Walters (28), Ivy (19), Best and Hicken). Similar obstruction caused by pancreatitis has been shown to occur by Thiessen and Walters (43).

From the Laboratory of Surgical Research, Department of Surgery, and the Institute of Pathology, Western Reserve University.

METHOD

In the first series of 5 dogs, under barbital anesthesia and with an intratracheal tube in place, the common bile duct was exposed. It was dissected completely free from surrounding tissue just proximal to its entrance into the duodenal wall. This portion was carefully selected so as to be distal to the juncture of the bile duct from the right lobe of the liver and the common duct. At this point a silver clip was placed around the duct so as to include the duct and a stylet measuring 1.8 millimeters in diameter. The ends of the clip were pressed firmly together and the stylet was removed, thus allowing the clip to remain in place. The abdominal incision was closed in the usual manner.

In the second series of 5 dogs the same procedure was carried out, but in addition a cholecystectomy was performed.

After operation the dogs were rarely sick, and food was taken on the first day. The diet was a standard one of cereal and meat scraps.

Samples of blood were taken in the fasting state before the operation, on the first, third, and seventh days after operation, and weekly thereafter for a total of 13 determinations on each dog over a period of 10 weeks. The coagulation time according to the method of Lee and White (25) was done at the time the blood was drawn. The number of red cells and the concentration of hemoglobin was determined. The remaining blood was then analyzed for cholesterol, cholesterol esters, total calcium, urea nitrogen, fibrinogen, and serum bilirubin stated as icteric index. The weight of the dog was noted at the time of each blood sampling. All stools were tested for the presence of bile by the Schmidt test to rule out the possibility of complete obstruction occurring.

OBSERVATIONS

There were no deaths in either series. One dog in the second series at the end of the second month developed a sudden increase in weight and what was thought to be ascites. The icteric index suddenly rose, although the animal's clinical condition remained excellent. The fluid wave in the abdomen disappeared just as suddenly and the jaundice receded. At the end of the period of observation the dog was sacrificed; the stomach was hugely dilated and contained several large pieces of bone which apparently had obstructed the pylorus and angulated the common duct.

Red cells and hemoglobin. All of the animals developed a drop in the red cell count and hemoglobin concentration. The dogs which had had the gall bladder out in addition to the obstruction showed a marked initial decrease, but after the first week the average variations were insignificant. The series of dogs with just the obstruction showed a slower but similar decline with the leveling of the curve occurring only after 3 weeks. The dogs in which the gall bladder had been removed did not show as great a total drop as those dogs with the obstruction alone.

Each animal over a period of 3 months lost approximately 400 cubic centimeters of blood. This loss in repeated amounts of 30 cubic centimeters does not seem great enough to explain the developing anemia. Snell, Greene, and Rowntree (40), after ligating the common duct and removing the gall bladder, noted a steady fall in the number of red cells with a slight reduction in hemoglobin. They attributed this result to repeated bleeding. Mann and Bollman refer to the anemia that is associated with liver injury. This may have been a factor in the present series in addition to the chronic blood loss.

Blood clotting. The coagulation time according to the method of Lee and White (25) was done each time blood was taken. The average coagulation time curve in the series with the gall bladder present showed a slight decrease, but the difference was not great. In general, the coagulation time showed no significant variation. In support of this observation none of the dogs showed any tendency to bleed. Lee and Vincent (24) have stressed the duration of jaundice as a factor in causing an increase in coagulation time. Since the icterus in these animals lasted only 2 to 3 weeks, a change was not to be expected.

Icteric index. In the first series with the gall bladder in place the maximum rise in the jaundice did not occur until the seventh day. When the gall bladder was removed, in addition to the obstruction to the common duct, the jaundice was highest in all but 1 of the animals from the third to the seventh day after operation. Thereafter, in both series the icteric index gradually diminished and returned to normal during the period of observation. This acute rise when the gall bladder was absent has been demonstrated previously; it was to be expected, since the gall bladder was not present to store the secreted bile. The speed by which obstruction to the common duct becomes apparent has been demonstrated by Snell and his co-workers (41). They found a direct van den Bergh reaction 1½ hours after ligation of the common duct and removal of the gall bladder while the serum bilirubin increased to 2.2 milligrams per 100 cubic centimeters in 4 hours.

Urea nitrogen. The blood urea nitrogen in both series showed an initial decrease, then a rise between the fourteenth and twenty-first days, and decreased from then to the end of the period of observation. These variations were more marked in the series with the obstruction present and the gall bladder removed. It is difficult to explain why the presence or absence of the gall bladder should make this difference. Since the values for the blood urea nitrogen varied conversely with the icteric index, some degree of temporary hepatic insufficiency is suggested as the cause. If this explanation is valid, the larger variations in the blood urea nitrogen in those dogs which had had the gall bladder removed in addition to the obstruction postulate a greater degree of early hepatic damage in that series. Previous observers have all demonstrated a decrease in the blood urea in the presence of jaundice or after hepatectomy (Yanagi and Bollman, Mann, and Magath).

At the end of the experiments the curves in both series approximated each other. It must be pointed out that all the values are within

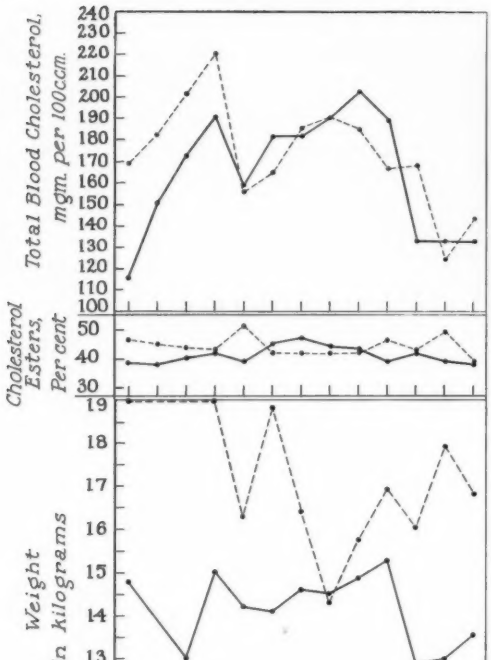

Fig. 1. Curves of average values. - - - - - - Series I, partial obstruction of common bile duct. ●——● Series II, partial obstruction of common bile duct with cholecystectomy.

normal limits, despite the observed rise and fall.

Calcium. The total blood serum calcium in the first series with only the obstruction showed a rise and then a fall. In the second series there occurred a slight steady rise, the significance of which is questionable.

The literature has many conflicting reports on both the quality and quantity of the blood calcium in jaundice (Ivy, 20). The presence of icterus has some effect on the metabolism of calcium as shown by the bony changes occurring in prolonged jaundice (Buchbinder and Kern, 9), by the greater tolerance of the jaundiced dog to intravenous calcium (Walters and Bowler), and by the decreased effectiveness of parathyroid extract in parathyroidectomized dogs with jaundice (Buchbinder and Kern, 10).

Fig. 2. The lower end of the common bile duct in 2 dogs, showing the strictures produced. On the left the silver clip has ulcerated through only partially.

Fibrin. The fibrinogen content of the blood increased in both series. Snell, Greene, and Rowntree (41) observed a sharp postoperative rise in blood fibrin after ligation of the common duct, followed by a decrease to the upper limits of normal. The changes observed are in accord with the belief that damage to the liver causes a rise in blood fibrinogen and fibrin.

Cholesterol and cholesterol esters. The values for total blood cholesterol varied similarly in both series. There was a rise to a peak at the end of 7 days, a sharp fall at 14 days, a secondary rise between the thirty-fifth and forty-second day, with a final drop to the pre-operative level (Fig. 1).

The cholesterol esters, on the other hand, reacted conversely in the two series. In the series in which the obstruction was present alone, the percentage of esters rose as the total cholesterol fell, and fell when the total cholesterol rose. When the gall bladder was removed, in addition to the presence of the partial obstruction, the changes in cholesterol esters paralleled the changes in total cholesterol (Fig. 1).

The significance of these changes is hard to evaluate. It is generally conceded that a rise in free cholesterol with a fall in the esters means liver damage (11, 14, 17, 23, 33, 37). In both the series of dogs one may postulate approximately an equal amount of ultimate liver damage. The difference, therefore, should be due to the presence of the gall bladder in the

TABLE I.—BLOOD CHANGES FOLLOWING PARTIAL OBSTRUCTION TO COMMON BILE DUCT

Time Days	Weight Kilos	Red blood cells Millions	Hemoglobin Gm./100 c.cm.	Coagulation time Seconds	Cholesterol total Mg./100 c.cm.	Cholesterol esters Per cent	Total calcium Mg./100 c.cm.	Icteric index	Blood urea nitrogen Mg./100 c.cm.	Fibrinogen Gm./100 c.cm.
Pre-op.	19.0	8.54	17.1	243	169	46.5	9.6	2.4	5.5	.346
1		8.09	16.1	205	182	45.0	9.8	3.5	6.0	.350
3		8.09	16.1	260	201	44.0	9.9	7.4	5.1	.380
7	19.0	7.75	15.8	251	220	43.0	11.0	14.3	6.3	.485
14	16.3	7.51	15.4	254	156	51.0	10.5	12.7	7.0	.388
21	18.8	6.45	14.0	250	165	42.0	10.8	8.6	6.2	.377
28	16.4	6.40	14.1	265	136	42.0	12.7	9.0	6.5	.450
35	14.3	6.65	14.4	216	190	42.5	9.7	7.4		
42	15.7	6.79	13.9	240	185	42.5	9.5	7.4		
49	16.9	6.82	14.4	226	167	46.0	8.6	5.3		
56	16.0	6.23	13.4	214	168	43.5	8.3	5.5		
63	17.9	6.26	11.4	217	125	49.0	8.7	3.0		
70	16.8	6.55	14.0	201	144	39.0	9.3	2.7	10.0	

first series. Sweet reported that after cholecystectomy the blood cholesterol rose and did not return to normal for 40 days. Previous experiments by many workers (1, 2, 4, 11, 12, 16, 18, 23, 31, 32, 33, 44) on the action of the gall bladder on cholesterol metabolism are contradictory; the best data appear to show that the normal gall-bladder mucosa may absorb small amounts of cholesterol, while the inflamed mucosa may add cholesterol to the gall-bladder bile by desquamation (Ivy, 19; Torinoumi). The changes described would signify then, that the rise in total cholesterol is in response to liver damage, while the change in the esters is caused by an absorption of cholesterol from the bile with the amount of the esters in the blood remaining the same. This resulted in a relative drop in the cholesterol-cholesterol ester ratio. When the total cholesterol value dropped, the percentage of esters remained more or less the same, and the relative increase of esters became apparent.

TABLE II.—BLOOD CHANGES FOLLOWING PARTIAL OBSTRUCTION TO COMMON BILE DUCT AFTER CHOLECYSTECTOMY

Time Days	Weight Kilos	Red blood cells Millions	Hemoglobin Gm./100 c.cm.	Coagulation time Seconds	Cholesterol total Mg./100 c.cm.	Cholesterol esters Per cent	Total calcium Mg./100 c.cm.	Icteric index	Blood urea nitrogen Mg./100 c.cm.	Fibrinogen Gm./100 c.cm.
Pre-op.	15.8	7.54	15.4	247	114	38.5	9.4	3.2	11.5	.235
1		7.86	16.0	216	150	38.0	9.8	44.3	8.4	.373
3	13.0	6.95	14.7	268	173	40.1	9.5	13.6	9.0	.346
7	15.0	6.51	13.6	264	190	42.0	9.7	14.0	8.0	.292
14	14.2	6.20	13.8	240	159	39.0	10.3	15.5	10.7	.333
21	14.1	6.78	14.0	232	181	45.0	10.4	9.4	11.2	
28	14.6	6.82	14.0	220	181	47.0	10.3	6.4	10.7	.420
35	14.5	6.11	13.4	250	190	44.5	9.9	7.2	8.85	
42	14.9	6.25	13.9	263	203	43.0	10.6	6.25	7.8	
49	15.3	6.37	13.4	228	189	39.0	10.1	5.6	8.5	.410
56	12.9	6.49	13.6	256	134	42.0	9.6	12.7	7.0	
63	13.0	6.92	13.4	298	134	39.0	10.4	6.5	8.0	
70	13.6	6.61	13.2	233	134	38.5	10.1	5.0	8.5	

It has been shown that during fat absorption the proportion of cholesterol esters is high (Bloor and Knudson, 7, 21; and Currie). Pathologically, cholesterol deposits may be seen in any tissue in which cells are undergoing destruction, and where absorption is poor (Wells). If these observations are accepted, it is quite possible that the rise in the level of the esters is an absolute one caused by degeneration of the liver secondary to obstruction.

The secondary rise in total cholesterol coming between the fifth and sixth weeks may have been due to the liver damage becoming more apparent before the healing process began.

It was suggested that the variations in cholesterol and its esters may have been due to the nutritional state of the animals. These variations of the serum lipoids with the state of nutrition have been studied (Man and Gildea, and Wendt). In general, during starvation an initial hypocholesterolemia occurred after which the cholesterol values varied with the state of nutrition. In both series of observations reported here, the initial drop in total cholesterol did not occur although there was a definite loss in weight. The total cholesterol rose until the seventh day. Thereafter, in the dogs with the partial obstruction present and the gall bladder removed, the two curves varied directly (Fig. 1). At the end of the period of observation, however, when the cholesterol returned to normal, the weight had fallen appreciably. In the series of dogs with only the obstruction, after the initial rise in cholesterol, the two curves varied inversely, similar to the cholesterol-cholesterol ester curves in the same dogs. From these results it cannot be said that the changes in the blood cholesterol were caused by the variation in the state of nutrition.

It is more probable that the changes in the total cholesterol are the result of the liver damage.

At the end of the experiment the presence of partial obstruction was proved at autopsy. All the dogs showed strictures at the point where the clip had been placed (Fig. 2). The clips had ulcerated through and in 4 dogs it was found lying free in the upper common duct. The bile back of the stricture contained small sandy particles and was turbid. The liver was cirrhotic in all the dogs. The pancreas was normal. The duodenum and stomach showed gross inflammation only in 2 dogs.

SUMMARY

A study of the comparative effects of partial obstruction to the common bile duct with and without cholecystectomy was made (Tables I and II). It was hoped that some help might be obtained in explaining symptoms arising from partial or recurring common duct obstruction in man. The observations in the main agree with those noted after ligation of the common duct, differing only in degree. A peculiar variation in the cholesterol-cholesterol ester ratio has been shown to occur. In the presence of obstruction and an intact gall bladder, the cholesterol esters increased when the total cholesterol decreased, and decreased when the total cholesterol increased. In the presence of obstruction and with the gall bladder removed, the cholesterol esters varied directly with the total cholesterol. The evidence favors the view that these variations result from damage to the liver with the gall bladder playing a secondary rôle, rather than from changes in the state of nutrition.

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THE EFFICACY OF PHENOL AND TETANUS ANTITOXIN IN THE TREATMENT OF EXPERIMENTAL TETANUS

WESLEY D. THOMPSON, Jr., M.D., and LEON FRIEDMAN, M.D., Philadelphia, Pennsylvania

THE use of phenol in the treatment of tetanus antedates the isolation and culture of the Clostridium tetani by Kitasato in 1889 (15). Gualdi, a student of Baccelli, in 1888 reported before the First Italian Congress of Internal Medicine, the excellent results obtained by him and Baccelli in the treatment of several hundred cases of neuralgia, sciatica, and other conditions by the injection of aqueous solutions of phenol. Finding the chemical to be a powerful analgesic and sedative, they were tempted to try it on a severe case of tetanus. The patient recovered. Baccelli became a staunch advocate of this type of treatment which has become identified with him to the extent that it commonly bears his name.

In his paper in 1911, Baccelli referred to the work of Kitasato (16) in 1891, and that of Babes (2) in 1892, as lending experimental support to the use of phenol in the treatment of tetanus. Kitasato discovered that phenol, when mixed with a filtrate from a culture of Clostridium tetani, *in vitro* would detoxify the toxin. He found that when equal amounts of a 3.0 per cent phenol solution and filtrate were combined and the mixture allowed to stand for one hour, 0.1 cubic centimeter of this solution would not cause tetanus when injected into mice. It required only .00001 cubic centimeter of the filtrate itself to kill a mouse in 5 to 6 days. Baccelli failed to mention in his paper that Kitasato also found other chemicals to be of benefit in even lower concentration. For example, hydrochloric acid was effectual in 0.5 per cent solution, cresol in 1.0 per cent solution, calcium hydroxide in 0.1 per cent solution, and sodium hydroxide in 0.3 per cent solution.

In referring to the work of Babes, Baccelli stated that this investigator found that he could immunize animals to tetanus with the blood or serum of several species of animals which had been previously "immunized" by injections of phenol. This "experiment" consisted in taking blood from the heart of a rat which had survived Clostridium tetani and phenol injections, and injecting this into two guinea pigs. Both animals were then injected with a culture of the Clostridium tetani. One survived. He obtained the same results using rabbits.

In 1898, Babes (3) summarized his experiments, stating that he had cured dogs which had been inoculated with a virulent culture of Clostridium tetani by injecting them five times daily with 25 cubic centimeters of a 0.5 per cent solution of phenol, even when the treatment was delayed until first symptoms appeared. All the control animals died but all of the treated dogs recovered in about 9 days. Relaxation of muscle spasm appeared first at the point of the phenol injections. Pigeons were also used; 6 were inoculated with a culture of Clostridium tetani, and as soon as the first signs of the infection appeared, 3 were injected 8 times daily with 1 to 2 cubic centimeters of a 1.0 per cent solution of phenol. The treated animals survived while the 3 controls died. Similar results were obtained in rabbits, but rats were rarely saved. The results in these experiments were much more constant than in similar experiments reported in 1892 in which he used a 1:1000 solution of phenol. In closing he said, "The general result of this treatment is very remarkable and hardly less manifest than the action of antitetanic serum. The animals cured were not, however, absolutely immune to new tetanus inoculations but succumbed after repeated injections of toxins."

It does not appear that any definite conclusions can be drawn from these experiments for Francis and Vaillard and Rouget found that tetanus spores in pure culture and free from

From the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania, Philadelphia.
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tetanus toxins when injected subcutaneously into guinea pigs and white mice, do not give rise to tetanus but lie dormant as inert bodies at the point of injection, awaiting either destruction by phagocytes or an awakening into activity and toxin production by tissue destruction or secondary infection. It would, therefore, seem that the symptoms of tetanus which Babes observed in his animals were due to the amount of toxin that was injected with the bacilli in the cultures, and the important factor of toxin content was not controlled. It is quite plausible that the animals receiving a sublethal amount of tetanus toxin survived, while those receiving a fatal dose died. That he was able to save 1 of 2 animals inoculated with a culture of Clostridium tetani following the injection of the blood of a rat which had survived inoculations of Clostridium tetani and phenol may be explained on the basis that either the toxin injected was of a sublethal quantity, or that there was sufficient antitoxin in the blood of the rat to render the recipient animals passively immune. Of course, both factors may have played a part. In either event, it would be impossible to state that the phenol played any significant rôle.

McClintock and Hutchings performed some experiments similar to those of Babes. In their first experiment they used 5 pigs and gave each subcutaneously ten times the minimal fatal dose of U. S. standard tetanus toxin. As soon as symptoms developed the pigs were given 0.5 cubic centimeter of a 2.0 per cent phenol solution subcutaneously every 2 hours during the day. All of the pigs died and no effect was observed. They repeated this experiment and gave the phenol every 2 hours day and night. In this experiment 2 of the pigs recovered. They again repeated the experiment, the phenol injections being started immediately after the injection of the toxin. In this case all of the pigs died. Similar results were obtained in experiments on sheep. It did appear to them that the sheep were less spastic when treated with phenol than with antitoxin.

Camus, working with dogs, found phenol of no value in treating tetanus, regardless of the amounts used, or at what stage of the disease the phenol was administered. He used tetanus toxin and a 3.0 per cent aqueous solution of phenol subcutaneously in varying amounts. The largest amount of phenol used was 20 cubic centimeters daily. The controls and the phenol injected dogs died in about the same time, i.e., 5 to 6 days. The dogs injected with phenol 24 hours after the administration of the toxin died at the same time as did the dogs which received the injections at the time the signs of generalized tetanus developed. Flores obtained similar results. He used 11 guinea pigs, giving each one a fatal dose of toxin intramuscularly, and at the first signs of tetanus administered a total of 3 cubic centimeters of a 1.0 per cent aqueous solution of phenol daily in fractional doses. Four of the guinea pigs died on the second day and the remainder on the third day. The 17 control animals died in 2 to 4 days; 14 of them on the third day.

It would seem from the 3 latter reports that the phenol treatment, as recommended by Baccelli, is of no benefit. However, there are many clinical reports of the cures of cases of tetanus with phenol injections, including a number of cases which had trismus and opisthotonos with generalized spasms. Most of the reports are based upon only 1 or 2 cases. Very few fatal cases have been reported in which this therapy was used. Baccelli, in 1911 (4), collected 190 cases from the literature from 1888 to 1911. These cases were from about one hundred different physicians. Baccelli divided the cases into groups. He classed 94 as severe, of which he stated 92 were cured, the mortality being decreased according to his calculation from 100 per cent to 2.12 per cent. He discarded from this group all cases which did not receive at least 1 gram of phenol per day. In the group that he classified as being very severe there were 38 cases, 11 of which, he stated, did not receive sufficient phenol. From the 27 cases that he thought did get sufficient phenol 22 were cured, a mortality, according to Baccelli, of 18.5 per cent. He stated that the average maximum dose was 1.5 grams of phenol per day, but often more was given. Single doses ranged from 0.1 to 0.15 gram. It was possible, however, to increase the dose in a 9 year old boy to 0.75

TABLE I.—RESULTS OF EXPERIMENTS WITH SUVANSA METHOD

Dog No.	Weight Kilo.	Tetanus toxin 100 D.L.D.* I. V. M.L.D.	Tetanus antitoxin			Phenol 1:400 0.57 c.cm./kg. intrathecally		Death from tetanus No. hours after toxin	Remarks
			Units I.V.†	Neutralizing doses Units	Time interval after toxin I.V. hrs.	c.cm.	No. hours after toxin		
405	7.7	369600 sol.						44¼	Onset of ascending tetanus in 25 hours.
447	7.5	360000 sol.						42	Onset of ascending tetanus in 26 hours.
823	9.8	470400 pulv.						25	Descending tetanus.
961	8.1	388800 pulv.						26	Onset of descending tetanus in about 16 hours.
418	7.3	350400 pulv.						25	Onset of descending tetanus in 19 hours.
975	8.5	408000 pulv.						26	Onset of descending tetanus in 19 hours.
448	9.3					5.3			Slight weakness right leg for few hours. Dog still O.K. 7 days later.
417	10.6					6.04			Slight weakness left hind leg for 2 days. Otherwise O.K.
382	8.6					4.9			No signs.
409	9.9	475200 sol.				5.66	6	35	Onset of ascending tetanus in 25 hours.
219	6.5	312000 pulv.				3.71	6	21½	Ascending tetanus.
594	7.4	355200 pulv.				4.23	6	20½	Descending tetanus.
450	9.3	446400 sol.				5.31	1½	31	Onset of ascending tetanus in 24 hours.
407	9.0	432000 sol.	86450	200	6				Died from distemper 7 days later. No tetanus.
449	9.1	436800 sol.	87360	200	6				Developed local tetanus at site of toxin injection 30 hours later. Never general tetanus.
639	9.5	456000 pulv.	91200	200	6				Died in 66 hours of severe intercurrent distemper.
406	9.2	441600 sol.	88270	200	6	5.26	6		Died from distemper 5 days later. No tetanus.
445	8.0	384000 sol.	75920	200	6	4.57	0		Died from distemper 11 days later. No tetanus.
448	8.7	417600 sol.	83460	200	6	4.97	0		Died from distemper 5 days later. No tetanus.

*1 dog lethal dose equals 480 minimum lethal doses per kilogram.
†1 unit neutralizes 1000 M.L.D.

gram every 12 hours, for 12 days. Other patients were given as much as 3.0 grams per day for 14 days without apparent harm. He, himself, used a 2.0 to 3.0 per cent aqueous solution, and gave not more than 0.3 to 0.5 gram the first day, but if the urine remained normal, he quickly increased the dose from 1.0 to 1.5 grams per day in divided doses. Woods used a 10 per cent solution and Maragliano used a 5 per cent solution in sterile oil to avoid the local effects of phenol, especially in newborn babies. In the very severe cases, Baccelli advised the immediate injection of 1 gram the first day.

As a result of Baccelli's paper there was from 1911 to 1914 a gradual increase in the publications of isolated cases of tetanus cured by phenol. However, from 1914 on the reported cases became rarer. Bruce, in 1915 (7) and 1916 (8), stated that magnesium sulphate and phenol had been used in the cases of tetanus in the home hospitals of England but had been found to be of no value. In the first report 7 patients died of those receiving subcutaneous doses of less than 16.2 grains of phenol per day, and 5 recovered, while of those receiving from 16.2 to 80.0 grains per day, 7 died and 6 recovered. In the second report about the same ratio prevailed. All of these patients also received tetanus antitoxin. Leishman and Smallman, in their analysis of the cases of tetanus in the British Expeditionary Forces in France, reported no favorable results from the use of phenol. However, they reported neither the amount of phenol used nor the method of administration. Stricker, writing on tetanus in Germany during the war, made no mention of the phenol

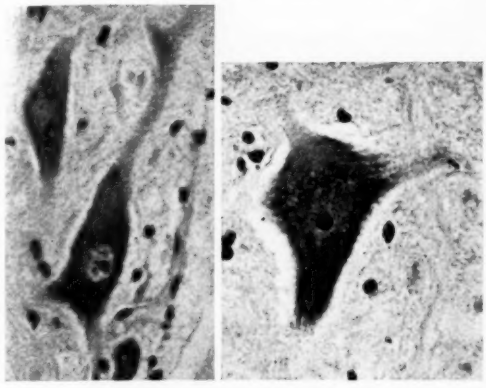


Fig. 1. Dog 418, cord. Received 100 D.L.D. of tetanus toxin (pulverized) intravenously. Sacrificed at 25 hours when near death. Anterior horn cells show acute cell disease with loss of Nissl substance and pale staining of cell prolongations far from the cell. The nuclear membrane is lost. a, left, ×500, cresyl violet stain. b, ×400, cresyl violet stain.

Fig. 2. Dog 382, cerebrum. Received 0.57 cubic centimeter of phenol (1:400) per kilogram of body weight intrathecally and was sacrificed at 72 hours. Thickening and edema of the meninges over the cortex. ×110, hemotoxylin and eosin stain.

treatment, and we have found no Italian report on wartime tetanus which mentions the Baccelli method. Corniglion stated that the French Army had been using phenol successfully both in prophylaxis and treatment but no mention was made of the dosage. He reported 4 patients who recovered after the administration once daily by either intramuscular or intravenous routes of 40 to 70 cubic centimeters of a 1.0 per cent aqueous phenol solution. It was, perhaps, as the result of war experiences that little appeared in the literature until 1931 when Suvansa published a report of 14 cases with only 4 deaths. Of the 4 that died 3 were moribund upon admission and 1 died from uremia. These results, compared with the poor results he had been getting with antitoxin therapy, led him strongly to advise its use. He administered intrathecally a 1:400 solution of phenol in normal saline in dosage of 30 to 40 cubic centimeters to adults and 12 to 20 cubic centimeters to children. Since the publication of this article he has had 12 additional cases (23) with 5 deaths and 7 recoveries from 1931 to 1934. However, from 1934 to the present time he has been able to obtain a larger supply of antitoxin and has used it with fairly good results, injecting 60,000 to 120,000 international units subcutaneously daily. He is still of the opinion that phenol can cure those conditions which are not too severe. He uses the pulse rate as a standard of severity. Patients who have a pulse rate of over 100 in adults or 120 in children (the pulse rate being taken between the spasms) he considers to have "severe" conditions. He further stated that tetanus resulting from wounds of the head and the neck is not amenable to phenol treatment. At the same time Pilloni reported the results of 53 cases of tetanus observed during the 12 previous years treated with phenol alone. Of the cases which had an incubation period of 3 days or less all died; from 3 to 10 days, 6 died and 8 survived; from 10 to 30 days, only 1 died out of 28. His maximum dose per day was 0.85 gram given subcutaneously in fractional doses, following the technique of Baccelli. He used no tetanus antitoxin.

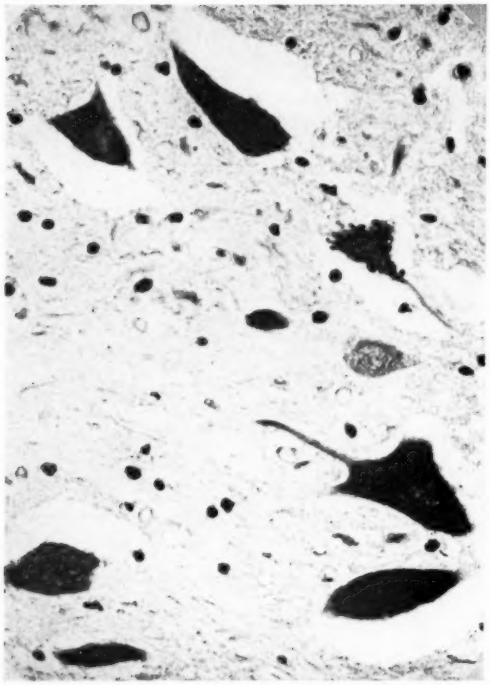


Fig. 3. Dog 450, cord. Received 100 D.L.D. of tetanus toxin (solution) intravenously and 6 hours later 0.57 cubic centimeter of phenol (1:400) per kilogram of body weight intrathecally. Dog died in 31 hours from tetanus. Anterior horn cells in toxic disease. Chromatin diffusely stained. Nuclei barely visible. One cell shows encrustation of pericellular glia network. ×440, hemotoxylin and eosin stain.

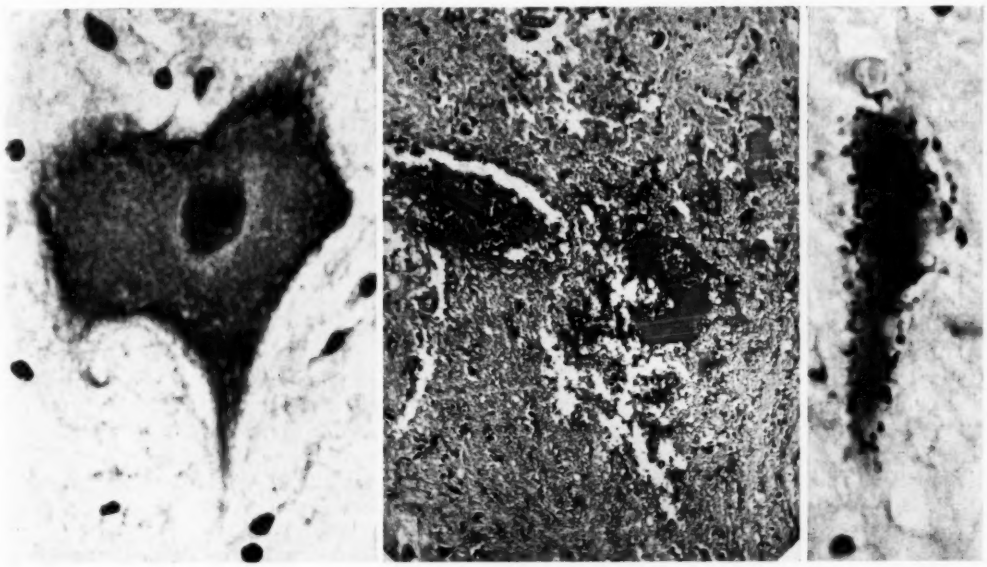
Three American authors reported favorable results following phenol and antitoxin treatment. Bryan reported 6 cases with 6 recoveries. He used the phenol intravenously in a 1.0 per cent solution, giving from 30 to 40 cubic centimeters every 8 hours. In addition, these patients received from 65,000 to 105,000 units of tetanus antitoxin. Bates reported 4 recoveries out of 5 cases following Baccelli's technique while Miller reported 1 successful case following the method used by Suvansa. Both of these authors also gave large doses of tetanus antitoxin in addition to the phenol. Prior to these reports, Beall in 1924 reported 8 successfully treated cases using 1 to 2 grains of phenol intramuscularly every 4 hours usually in a 15.0 per cent aqueous solution. In addition his patients received 30,000 units of tetanus antitoxin on the first day. They all had trismus and convulsions. The incubation periods were reported in 5 cases and ranged from 2 to 12 days.

In many of these cases the tetanus antitoxin alone might have effected a cure, regardless of the amount of phenol given, yet it is not possible to state that the phenol did not supplement the antitoxin.

What can we conclude from these reported clinical successes? A patient will not succumb to tetanus unless he gets a full lethal dose of the toxin, but just what a lethal dose is for man we do not know. There is no doubt that it will vary with the individual due to difference in host resistance. Furthermore, there is no test by which we can tell just how much toxin the patient has fixed or will absorb. Following the clinical course of the disease may help but little, because we never know the exact incubation period, the number or virulence of the Clostridium tetani, or their rate of toxin production. If we knew these facts we could then better prognosticate in the individual case. Even though it is, theoretically, possible for a patient to absorb and fix seven-eighths of a fatal dose of toxin and not die, it is hardly possible to believe that all of the cases reported as having been cured by phenol alone would fall into this group. Because of the great expense involved in the treatment of tetanus with adequate amounts of tetanus antitoxin, we felt that it would be of importance to carry out some controlled experiments in an attempt to determine the value of phenol in the treatment of experimental tetanus, alone and in combination with antitoxin.

PART I

Method. We first investigated the method advocated by Suvansa (23). We assumed that he would use his maximum dose of 40 cubic centimeters in treating a young, well developed man of 150 pounds with a severe case of tetanus. From this we obtained our intrathecal dose of 0.57 cubic centimeter per kilogram of body weight of a 1:400 phenol solution in normal saline. We desired to use a dose of tetanus toxin that we knew would kill the dog, regardless of the amount of tetanus



a b c

Fig. 4. Dog 594, cord. Received 100 D.L.D. of tetanus toxin (pulverized) intravenously and 6 hours later 0.57 cubic centimeter phenol (1:400) per kilogram of body weight intrathecally. Dog died in 20½ hours from tetanus. Acute cell disease in anterior horn cell with loss of Nissl substance, pyknosis of nucleus and swelling of nucleolus. a, ×840 cresyl violet stain. b, Thrombosis and liquefaction of gray matter around it. ×105. c, Incrustation of pericellular glia network around degenerated anterior horn cells. ×840.

antitoxin administered. Abel and Chalian had found that if 100 D.L.D.[1] of tetanus toxin were injected intravenously and 6 hours allowed to elapse, no amount of tetanus antitoxin could save the animal. We, therefore, decided to use this amount, since we felt that by so doing we could tell whether phenol was of any benefit in extreme tetanus, either alone or in combination with tetanus antitoxin.

Experimental data. Healthy, young, adult dogs were used for each group of experiments. A complete autopsy was performed on each animal that died or was sacrificed.

Experiment 1. (1) The length of time required for dogs to die after the intravenous administration of 100 D.L.D. of tetanus toxin was determined. The symptomatology was carefully observed in the 6 dogs as tetanus developed. (2) The effects of intrathecally administered phenol (1:400) given in the dosage of 0.57 cubic centimeter per kilogram of body weight were studied in 3 dogs to which no toxin was given. (3) Three dogs were given intravenously 100 D.L.D. of tetanus toxin, and at the end of 6 hours were given intrathecal injections of phenol (1:400) in the same dosage as stated. The progress of the disease and the length of time that the dogs survived were noted. (4) Three dogs were prepared as in the third group, but instead of intrathecal phenol they were given at the end of 6 hours 200 times the neutralizing dose[2] of tetanus antitoxin intravenously and the subsequent course observed. (5) In 1 dog we combined the above 2 forms of therapy so that at the end of 6 hours the dog, which had received 100 D.L.D. of tetanus toxin, was given both intrathecal phenol as in No. 3, and 200 times the neutralizing dose of tetanus anti-

[1]From Abel and Chalian "We have found in the course of very numerous experiments extending over a period of 5 years that injection of 480 guinea pig L. D. 50's per kilogram invariably induces fatal tetanus in dogs of medium weight and age, and have, therefore, arbitrarily chosen this figure as our lethal dose for dogs. This dose kills dogs at random in from five to nine days."

[2]According to the United States Government standard, one unit of tetanus antitoxin will neutralize 1000 minimal lethal doses of tetanus toxin. Therefore, 200 times the neutralizing dose would be 200 times the amount of tetanus antitoxin which would be necessary to neutralize the total injection of the tetanus toxin.

toxin as in No. 4. All of our intrathecal administrations were made through the lumbar route with a regular spinal puncture needle while the dogs were under ether anesthesia.

This series of experiments (Table I) revealed that dogs given 100 D.L.D. of tetanus toxin invariably died in 25 to 26 hours when the freshly prepared dry toxin was used, and in 42 to 44 hours when the toxin in solutions (of equal strength when prepared sometime prior to the experiment) was used. Histological study of the central nervous system revealed the toxic myelopathy so often described in tetanus (Fig. 1), while that of the kidneys revealed a simple nephrosis with passive congestion; the livers, an acute passive congestion with parenchymatous degeneration most marked in the central zones. Dogs given phenol alone intrathecally showed no clinical effects, but the histological study of the cord and brain after the phenol was injected revealed a thickening of the meninges (Fig. 2), the kidney, a mild simple nephrosis, and the liver, a mild cloudy swelling. The dogs given tetanus toxin intravenously, plus phenol intrathecally, died about 5 hours sooner than the controls. Histological study of the central nervous system here revealed a toxic myelopathy greater than that observed with tetanus toxin (Figs. 3 and 4). However, the kidney and liver showed much the same pathological picture as that found with toxin alone. The dogs which were given 100 D.L.D. of tetanus toxin, and then after 6 hours treated with 200 neutralizing doses of tetanus antitoxin, did not die of tetanus as predicted by Abel and Chalian. One dog survived and showed no ill effect whatsoever from the tetanus toxin and was in excellent condition when returned to stock 1 month later. Another dog developed local tetanus in the injected hind limb and was sacrificed at the end of 11 days. It at no time showed any signs of generalized tetanus. The remainder of the dogs died from intercurrent infection, yet all but one lived sufficiently long after tetanus was expected to develop to preclude its subsequent development.[1] In the last phase only 1 dog was given similar amounts of tetanus toxin and then treated at the end of 6 hours with both phenol and tetanus antitoxin. As would be expected from the above, it also showed no signs of tetanus, but died from an intercurrent infection, yet sufficiently long after the experiment was started similarly to preclude any development of tetanus. None of these dogs showed any of the neurological involvement seen in tetanus.

These experiments demonstrated that dogs given overwhelming doses of tetanus toxin, known to kill healthy dogs in from 24 to 26 hours, are not helped. If anything, their death is hastened by additional central nervous system damage or lowered resistance to distemper, when given phenol intrathecally 6 hours after the tetanus toxin is given intravenously; while the use of tetanus antitoxin alone in sufficient amounts can save the dogs when given 6 hours after the toxin.

Experiment 2. In this group of dogs, we administered the same dosage of tetanus toxin and phenol as in the first experiment, but instead of waiting 6 hours to inject the phenol, we administered it as soon as possible after the toxin injection. The results, both as to the length of time before death from tetanus and to the histological findings, were similar to the findings in the first experiment.

PART II

We felt that the above experiments revealed that phenol administered intrathecally in the amounts used was of no value in neutralizing or detoxifying large doses of tetanus toxin given intravenously to dogs, regardless of the time of administration. We, therefore, began our investigation of the intravenous use of phenol as advocated by Corniglion and Bryan.

Method. These authors have found clinically that fairly large amounts of a 1.0 per cent phenol solution were compatible with life. We, therefore, adopted this percentage. Our solution was made by adding the required amount of liquid phenol of a known concentration to normal saline just prior to its use.

[1]Under similar circumstances, we have found that if the dogs did not show signs of tetanus within 5 days, they would not subsequently develop them. We, therefore, classed all dogs that lived 5 days as saved from tetanus, although they may have succumbed at that time or later from another infection. The first signs of distemper noted were purulent discharges from the nose and eyes. These were followed by a cough, loss of appetite, and general debility. Of the dogs that died or were sacrificed, varying degrees of pulmonary disease were found at postmortem. These changes ranged from a simple bronchitis with pulmonary congestion to obar or lobular pneumonia with abscess formation.

TABLE II.—RESULTS WITH PHENOL ADMINISTRATION

Dog	Weight	Phenol intravenously			Tetanus toxin intravenously				Result	
No.	Kilo	gms./K	1% Phenol c.cm.	Duration of I.V. minutes	Dog lethal doses*	M.L.D. gms.	Dissolved in P.S.S.	Duration of I.V. minutes	Death	Hours
253	10.6	0.25	265	105					Sacrificed Good condition	94
255	11.0	0.30	330	120					Sacrificed Distemper	94
256	8.0	0.35	280	190					Died Phenol	<18
292	8.8	0.40	352	200					Died Phenol	<18
204	6.0				100	288000 1.152	200	35	Died Tetanus descending	>26 <30
207	9.3	0.107	100	23	100	446400 1.786	100	15	Died Tetanus descending	>26 <30
202	7.0	0.143	100	44	100	336000 1.344	100	50	Died Tetanus ascending	>26 <30
235	9.3				10	44640 0.1786	200	45	Died Tetanus descending	>46 <50
208	8.5	0.117	100	145	10	40800 0.1632	100	145	Died Tetanus descending	>58 <66
218	8.0	0.125	100	115	10	38400 0.1536	100	115	Died Tetanus descending	>49 <57
219	8.5	0.117	100	100	10	40800 0.1632	100	100	Died Tetanus descending	>57 <65
233	9.3				10	44640 0.1786	400	80	Died Tetanus descending	>65 <68
234	9.0	0.222	200	70	10	43200 0.1728	200	70	Died Tetanus ascending	>46 <48
293	9.6	0.30	288	165	10	46080 0.1844	100	145	Died Tetanus	<50 >57
254	10.4	0.35	364	205	10	49920 0.1997	100	155	Died Phenol	>18 <24

*1 dog lethal dose equals 480 minimum lethal doses per kilogram.

This solution was administered intravenously into one of the hind legs by means of a closed drip method, thereby assuring a more accurate rate of flow. In the dogs which received both tetanus toxin and phenol, the toxin was administered similarly and simultaneously into the vein of the opposite hind limb. In each instance both flasks and tubings were filled and rinsed with a constant amount of normal saline, and the solution volume of phenol and toxin was kept equal. By so doing our dilution factor was kept constant in each dog. There were two exceptions to this in Experiment 3. The dogs that received 0.3 and 0.35 gram of phenol per kilogram of body weight were given tetanus toxin in dilution of only 100 cubic centimeters because of the large volume of phenol. The rate of administration depended upon the size of the dog and the total volume of fluids given. This rate varied from 23 to 205 minutes.

Experiment 1. It was first necessary to determine the tolerance of dogs for 1.0 per cent phenol given intravenously. We found (Table II) that the animals could tolerate 0.25 and 0.30 gram of phenol per kilogram of body weight; however, they succumbed to phenol poisoning when given 0.35 or 0.40 gram per kilogram of body weight. Death occurred in less than 18 hours. The first toxic manifestations to appear were convulsive tremors of the extremities which later became generalized during the administration of the phenol. In the animal which received 0.40 gram of phenol opisthotonos developed. In addition to tremor, salivation was marked. After the completion of the injection, the animals were unable to stand and would remain in any ab-

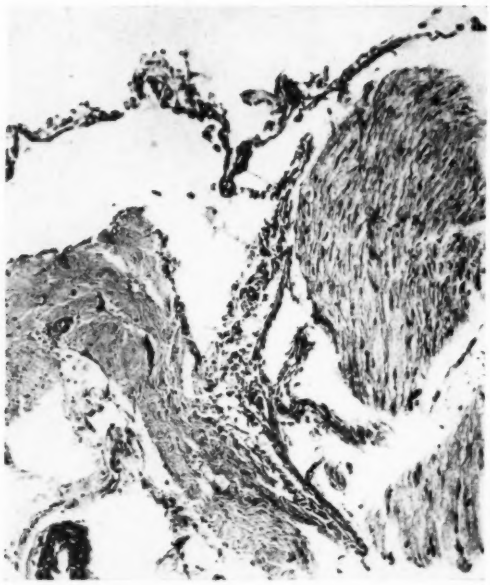


Fig. 5. Dog 926, cord. Received unpreserved tetanus antitoxin intrathecally and was sacrificed at 72 hours. Mild lymphocytic infiltration in the arachnoid around an anterior nerve route. ×295, cresyl violet stain.

normal position in which they were placed. Within 6 to 8 hours marked conjunctival edema was noted which in some cases resulted in a complete obliteration of the pupil. In the animals which received lethal doses of phenol these signs were progressive until death, while in the others the signs were less severe and entirely disappeared within 24 hours. Histological examination of the sections taken from the kidneys and livers revealed a simple nephrosis and mild cloudy swelling. These findings were, of course, most marked in the dogs receiving the larger amounts of phenol. We concluded that in dogs the lethal dose of 1.0 per cent intravenous phenol was between 0.3 and 0.35 gram per kilogram of body weight, and that the damage to the kidney and liver was in direct proportion to the amount of phenol given.

Experiment 2. The purpose of these experiments was to determine whether or not the intravenous injection of phenol in one hind limb would prevent or prolong the appearance of tetanus when 100 D.L.D. of tetanus toxin was simultaneously injected into the vein of the other hind limb. Because of the known damaging effects of both tetanus toxin and phenol, we decided to use a dosage of phenol which in itself had minimal effects. Bio-assays were run on the bloods from all the dogs.[1] The blood samples were taken in each instance at the conclusion of the injections. There were 3 dogs in this group (Table II), one control and two dogs receiving both phenol (0.107 and 0.143 gram per kilogram of body weight respectively) and tetanus toxin. All three of these animals died between 26 and 30 hours and all of the bio-assay determinations were found to be equal. Histological changes in the kidneys and liver were about the same as in the preceding experiment. We therefore concluded that intravenous 1.0 per cent phenol in the dosage mentioned, given simultaneously with 100 D.L.D. of tetanus toxin through opposite veins in the same fluid volume, did not alter the progress of tetanus and the bio-assays did not reveal any detoxifying effect of the phenol.

Experiment 3. Although the above experiments were negative, we decided to repeat them but using only 10 D.L.D. of tetanus toxin. In this series we had 2 controls and 6 experimental dogs (Table II) which received, respectively, in addition to the toxin, 0.117, 0.117, 0.125, 0.222, 0.30, and 0.35 gram of phenol per kilogram of body weight. The controls died of tetanus in from 46 to 68 hours; the phenol dogs died of tetanus in from 46 to 66 hours with the exception of the last dog that received 0.35 gram of phenol per kilogram of body weight. This dog died in about 20 hours from phenol poisoning. The bio-assays in all the animals remained equal except in the 2 dogs which received larger amounts of phenol, and in these, the bio-assays showed their blood to be more toxic for guinea pigs than that of the controls. It was noted in experiment 1 that in a normal dog the maximum tolerance was between 0.3 and 0.35 gram of phenol per kilogram of body weight. During this series it was found that the time of death of the last animal was approximately the same as that of the dog which received 0.35 gram of phenol

[1]The authors are deeply indebted to Dr. F. G. Jones of the biological division of the Lilly Research Laboratories for his co-operation in testing our blood samples.

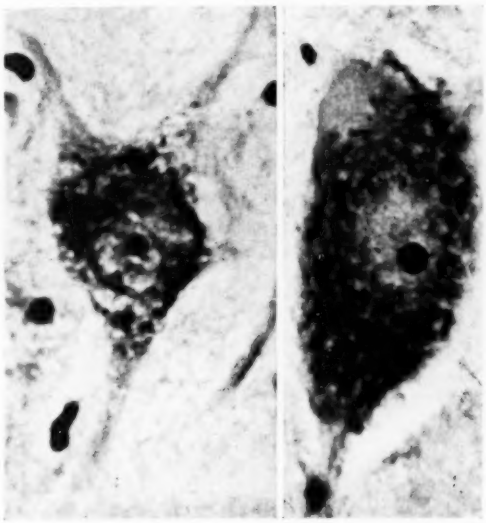


Fig. 6, left. Dog 963, cord. Received merthiolate preserved tetanus antitoxin intrathecally and was sacrificed at 72 hours. Acute necrosis of an anterior horn cell with vacuolization and hydropic swelling. ×975, cresyl violet.

Fig. 7. Dog 966, cord. Received cresol preserved tetanus antitoxin intrathecally and was sacrificed at 72 hours. Mild toxic disease of anterior horn cell with loss of nuclear membrane in an otherwise well preserved nerve cell. ×975, cresyl violet stain.

alone. It was thus indicated that the tolerance for phenol is not increased in cases of tetanus as claimed by Baccelli and others. The histological study of the kidneys and livers of these animals revealed varying degrees of simple nephrosis and passive congestion of the liver. We concluded that 1.0 per cent phenol administered intravenously in sublethal quantities simultaneously with 10 D.L.D. of tetanus toxin through opposite veins, the fluid volume of each being the same, did not alter the progress of tetanus and bioassays did not show detoxifying effect of phenol.

PART III

Realizing that the commercial preparations of tetanus antitoxin available for the treatment of tetanus are preserved with either 0.5 per cent phenol, 0.35 per cent cresol, or 1:10,000 merthiolate, and since this concentration of phenol is approximately twice that used by us in these experiments, it seemed

Fig. 8. Dog 962, choroid plexus. Received phenol preserved tetanus antitoxin intrathecally and was sacrificed at 72 hours. Focus of inflammatory infiltration with keratinization and loss of covering of plexus cells. ×95, cresyl violet stain.

advisable to inject these different preparations intrathecally in amounts proportional to the phenol previously used in Part I, i.e., 0.57 cubic centimeter per kilogram of body weight. This was done, and unpreserved horse serum was used as a control. None of the dogs showed any clinical evidence of ill effects and were sacrificed 72 hours after the injection. Microscopic sections showed the following: unpreserved horse serum (Fig. 5)—normal with the exception of a mild meningeal irritation; merthiolate preserved (Fig. 6)—acute, mildly toxic nerve cell disease; cresol preserved (Fig. 7)—subacute, mildly toxic irritation of nerve cells throughout the central nervous system; and phenol preserved (Fig. 8)—acute, mildly toxic nerve cell changes. The variations between the preserved specimens are of only academic interest. All the tested preservatives must be grouped as definite irritants. We therefore concluded that if a surgeon feels that tetanus antitoxin should be given intrathecally, non-preserved serum had best be used.

PART IV

Experiment 1. Because our findings did not agree with those of Abel and Chalian as to the preventability of tetanus 6 hours after the intravenous injection of 100 D.L.D. of tetanus

TABLE III.—RESULTS OF NEUTRALIZING DOSES OF TETANUS ANTITOXIN

Dog No.	Weight Kilo	Tetanus toxin 100 D.L.D.* I.V. M.L.D.	Tetanus antitoxin		Death from tetanus	Remarks
			Units I.V.† 6 hours after toxin	Neutralizing doses Units	No. hours after toxin	
819	8.0	384000 pulv.	9600	25	38.5	Tetanus descending.
820	10.0	480000 pulv.	24000	50	60	Tetanus descending.
964	6.0	288000 pulv.	28800	100	56	Tetanus descending.
821	7.4	355200 pulv.	35520	100	73	Tetanus descending.
822	7.2	345600 pulv.	51840	150	77.5	Tetanus descending.
887	8.2	393600 pulv.	72000	182	153	Tetanus descending.
886	9.0	432000 pulv.	78750	182	No tetanus	Returned to stock 1 month later.
407	9.0	432000 sol.	86450	200	No tetanus	Died 7 days later of distemper.
449	9.1	436800 sol.	87360	200	No tetanus	Developed local tetanus site of toxin injection. Killed 11 days after toxin given.
639	9.5	456000 pulv.	91200	200	No tetanus	Died in 66 hours of distemper.
314	11.8	566400 pulv.	7 hours after toxin 169920	300		Developed stiffness hind limbs and back 3rd day. No further advancement. Sacrificed 14th day because of intercurrent infection.
315	12.8	614400 pulv.	184320	300	144	Developed stiffness hind limbs and back 3rd day, opisthotonos 4th. No further advancement. Signs seemed to be lessening when found dead 6th day.
317	12.8	614400 pulv.	184320	300		Developed stiffness hind limbs and back 3rd day. No further advancement. Complete recovery.

*1 D.L.D. equals 480 M.L.D./Kg. †1 unit neutralizes 1000 M.L.D.

toxin, we injected a group of dogs with this amount of toxin and after 6 hours gave intravenously various neutralizing doses of tetanus antitoxin (Table III). It was found that the time of death of these animals was almost in direct proportion to the amount of antitoxin administered, e.g., the dog which received 25 times the neutralizing dose of tetanus antitoxin died from tetanus in 38½ hours, while the animal that received 150 times the neutralizing dose died in 77½ hours. Of the 2 animals which received approximately 182 times the neutralizing dose, 1 showed the first signs of tetanus in 51 hours and died in about 153 hours, while the other dog gave no evidence of tetanus and was returned to stock 1 month later in perfect condition.

These data with those derived in Part I, experiment 1, led us to conclude that dogs given 100 D.L.D. of tetanus toxin could be saved if between 182 and 200 times the neutralizing dose was given at 6 hours.

Experiment 2. Since it appeared that dogs given 100 D.L.D. of tetanus toxin intravenously had not irreversibly fixed one lethal dose of toxin within 6 hours, we decided to prolong the waiting period to 7 hours. Similarly we also increased the dosage of tetanus antitoxin from 200 times the neutralizing dose to 300 times, because our experience in the past has shown that the dosage of antitoxin must be proportionately increased with the time interval if the animal is to be saved. To 3 dogs, therefore, we gave 100 D.L.D. of tetanus toxin intravenously and at 7 hours gave, in a similar manner, 300 times the neutralizing dose of tetanus antitoxin. The course of these animals was uneventful until the third day when all 3 developed stiffness of the back and hind limbs (ascending tetanus was not uncommon in our experience). In 2 of the animals the signs did not progress; however, in 1 opisthotonos with inability to stand developed on the fourth day. The signs in this last dog remained stationary after the fourth day and seemed to be improving, but the animal was found dead on the morning of the sixth day. Of the 2 other dogs, 1 developed distemper

and was sacrificed on the fourteenth day because of its poor condition. The remaining dog gradually lost the spasticity and was in excellent condition when sacrificed 3 months later. Histological examinations of the kidney and liver were normal. There was, however, considerable thickening of the dura with mild infiltration of arachnoid, but the anterior horn and cortical cells appeared to be normal.

We concluded from these experiments that dogs can frequently be saved when 300 times the neutralizing dose of tetanus antitoxin is administered intravenously 7 hours after the intravenous injection of 100 D.L.D. of tetanus toxin, although signs of tetanus may develop. We must assume that some of the toxin was so fixed within 7 hours that 300 times the neutralizing dose of antitoxin could not inactivate it. The histological study of the surviving animal which was sacrificed 3 months later revealed that most of the pathological changes induced by tetanus toxin were reversible.

SUMMARY AND CONCLUSIONS

1. Intrathecal administration of phenol to dogs given intravenously 100 D.L.D. of a tetanus toxin known to kill healthy dogs within 25 to 26 hours, will not prevent death of the animals. If anything, their death is hastened by the additional central nervous system damage or lowered resistance to distemper which phenol apparently produces. The administration of tetanus antitoxin in sufficient amounts does save the dogs when given within 6 hours of a similar dose of toxin.

2. The lethal dose of a 1.0 per cent phenol solution for dogs was found to lie between 0.3 and 0.35 gram per kilogram of body weight when given intravenously. The damage to the kidneys and livers was in direct proportion to the amount of phenol given.

3. Intravenous 1.0 per cent phenol in the dosage used, given simultaneously with 100 D.L.D. of tetanus toxin through opposite veins, did not alter the progress of the tetanus and the bio-assays did not reveal any detoxifying effect of the phenol.

4. Intravenous 1.0 per cent phenol in the dosage used, given simultaneously with 10 D.L.D. of tetanus toxin through opposite veins, did not alter the progress of the tetanus and the bio-assays did not reveal any detoxifying effect of the phenol.

5. The common preservatives used in tetanus antitoxin are definite irritants to the central nervous system. Tetanus antitoxin containing these preservatives should not be used intrathecally in the treatment of tetanus.

6. Dogs given 100 D.L.D. of tetanus toxin intravenously were saved when given at 6 hours between 182 and 200 times the neutralizing dose of tetanus antitoxin.

7. Dogs given 100 D.L.D. of tetanus toxin intravenously were saved when given at 7 hours 300 times the neutralizing dose of tetanus antitoxin, although signs of tetanus developed. It was suggested that in 7 hours a portion of the injected tetanus toxin was so irreversibly fixed that it could not be neutralized by the dosage of antitoxin given.

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ECLAMPSIA AND POSTECLAMPTIC HYPERTENSION

A Follow-up Study with an Analysis of Factors Affecting the Remote Prognosis

LEON C. CHESLEY, Ph.D., and WILLARD H. SOMERS, M.D., Jersey City, New Jersey

IN the present paper, we shall present an analysis of a large series of posteclamptic women. Of the 167 patients who were treated in 169 eclamptic pregnancies in the whole experience of the Margaret Hague Maternity Hospital, 165, or 98.8 per cent, are either dead or have been re-examined recently. In addition, 20 women having had eclampsia elsewhere have been examined. We shall describe the incidence of hypertension and proteinuria, the results of renal function tests, the eyeground findings, and the general cardiovascular status at follow-up. An analysis will be shown of the several factors in pregnancy conceivably affecting the remote prognosis. Fetal mortality has been examined for the elements which seem to be of decisive importance.

As early as 1851, Frerichs concluded that eclampsia not infrequently gives rise to "chronic nephritis." Many writers, especially in Germany, have supported this opinion, while others have discounted it. Reviews of earlier publications and references to the literature have been given by Koblanck (1894), Schultz (1932), Bell (1932), Seidentopf and Major (1936), and Browne and Dodds (1939). In summarizing the earlier publications, Bell concluded that a mild degree of change in the renal blood vessels may often be present after eclampsia.

Whether the renal lesions, or the hypertension, found after eclampsia may be attributed to the toxemia is not entirely clear for at least two reasons: (1) In some patients, vascular disease and hypertension have antedated the eclampsia, as Teel and Reid have recently emphasized. (2) In many of the follow-up studies, posteclamptic patients have been re-examined 15 to 20 years after the eclampsia. As Volhard has said of hypertension, "the only etiological factor about which there can be no doubt is age." Without accurate determination of the incidence of hypertension in posteclamptics within periods too short for other factors significantly to affect the incidence, and without a suitable control series—almost never provided—it is hard to say that a hypertension found so many years after eclampsia has been caused by the toxemia.

Estimates of the frequency of permanent hypertension after eclampsia range from 0 to 78 per cent, with all intermediates, and with very few authors agreeing upon even the approximate incidence. Table I summarizes much of the published literature. A study of this table reveals that most investigations have been made by re-examining only a small proportion of the eclamptics originally observed.

Possible reasons for the wide discrepancies may be classified as: (1) Often a fair sampling of the posteclamptic population has not been made. (2) The majority of studies have been made with fewer than 50 patients. (3) The length of follow-up varies greatly; furthermore the incidence of hypertension increases with age in women as well as in men, and also the question of slow healing of the vascular lesions with the eventual disappearance of hypertension has a bearing upon the problem of the frequency of sequelae.

Heynemann and others have shown that after eclampsia many patients with residual hypertension gradually improve. On the other hand, Peckham re-examined posteclamptics at 13 months and again at about 6 years after delivery, and found that the incidence of "chronic nephritis" had increased from 23 per cent to 37.7 per cent. It would seem, therefore, that variations in the time intervals of follow-up observations will affect the incidence found for hypertension.

From the Margaret Hague Maternity Hospital.

Several writers have demonstrated that the earlier the onset of toxemia in the pregnancy, or the longer its duration, the more likely the patient is to have sequelae. Naturally the earlier the onset, the longer the patient is carried; conversely, the patients who are carried for long periods are those in whom toxemia appears early. However, in other publications, these two factors—duration of toxemia and time of onset—have not been separated in analyzing their influence upon the incidence of permanent hypertension. We have attempted such a differentiation.

If the duration of the toxemia *per se* affects the incidence of residual hypertension, then the treatment of eclampsia occurring before term must often include a balancing of the remote maternal interests against the welfare of the fetus. Published data upon which to base such calculations are meager.

MATERIAL AND METHODS

From the opening of the Margaret Hague Maternity Hospital on October 16, 1931, until December 31, 1939, there have been 42,476 deliveries therein. In this number 169 cases of eclampsia have occurred in 167 women; this gives an incidence of 0.395 per cent, or 1 in 253 deliveries. This figure happens to coincide exactly with the average hospital incidence cited by Hinselmann in his collective review. Of these 167 women, 20 are now known to be dead, 141 have been re-examined in 1940, and an additional 4 have been followed for at least a year before they were lost. Only 2 patients have had no follow-up. Thus 98.8 per cent of the patients are accounted for.

Needless to say, many patients were found only with difficulty. Nearly 6 months were spent in tracing and re-examining these women. Although public and private agencies located many addresses, the most fruitful method of finding the lost patients was by personally combing the apartment houses and neighborhoods in which they had lived at the time of hospital admission.

When patients did not report for examination, after a series of letters, home visits were made and blood pressure readings and urine specimens were obtained. If they did report, the examination also included eyeground readings, estimation of cardiac size, by palpation of the point of maximal impulse or by 6 foot x-ray plates, blood chemistry, and urea clearance tests.

After quiet reassurance, blood pressures were read with a mercury sphygmomanometer, with the patient lying down. After a rest interval of 5 minutes, the pressure was checked. The lower systolic and diastolic readings are reported here. The diastolic pressure was taken as the point at which the sounds suddenly become dull and muffled.

Urinary protein was determined by the sulfosalicylic acid method. Blood and urine areas were measured by Van Slyke's manometric procedures. In most cases the urinary output was sufficient to permit the calculation of maximal urea clearances; voided urines were used; patients were ambulatory.

RESULTS

An extensive analysis of the eclamptic pregnancies has been made in assessing the effects of various phases of pregnancy and eclampsia upon the findings at follow-up.

Immediate maternal mortality. Among the 169 cases of eclampsia, there were 12 immediate maternal deaths. This includes emergency admissions of patients who died within a short time and those dying from all causes. The gross maternal mortality is, therefore, 7.10 per cent. These maternal deaths were distributed as follows: (a) 4 deaths in 83 clinic cases, mortality 4.82 per cent; (b) 3 deaths in 46 private cases, mortality 6.52 per cent; (c) 5 deaths in 40 nonclinic cases, mortality 12.5 per cent.

The maternal mortality among the 114 primiparae, who made up 68.0 per cent of all cases, was 4.4 per cent. Of the 55 multiparae, 12.7 per cent died—7 cases.

In the period of this survey, there were 145 maternal deaths from all causes, many being unrelated to pregnancy. Of all these deaths, eclampsia caused or contributed directly to 8.28 per cent.

Fetal mortality. The total loss of babies, including abortions, stillbirths, neonatal deaths, and undelivered babies of mothers dying of antepartum eclampsia, was 33.5 per cent. If

TABLE I.—SUMMARY OF THE LITERATURE DEALING WITH THE SEQUELAE OF ECLAMPSIA

Author	Year	Clinic	Period	Cases of eclampsia	Survivors	Remote deaths	Re-examined	Length of follow-up	Incidence of			Pregnant again	Recurrence of toxemia
									Hypertension	Proteinuria	Chronic nephritis		
									Per cent	Per cent	Per cent		Per cent
Koblanck	1894	Berlin	1889–1894	?	?	?	77	6 wks.–5 yrs. +		16.9	6.5	16	6.3
Le Page	1912	Baudelocque	1884–1912	?	?	?						38	55.4
Baisch	1913	Munich	1902–1913	129	97	6	60	to 11 yrs.			10.0		
Wolff and Zade	1914	Heidelberg	1909–1913	52	43	?	23	?	8.7	4.3	8.7	8	50.0
Caldwell and Lyle	1921	New York	1918–1919	34	25	1	22	16–33 mos.			9.0	9	22.0
Gibson	1921	Chicago	1912–1920	?	?	1	14	1 yr. plus	50.0	28.5		7	100.0
Harris	1924	Baltimore	1919–1923	51	42	?	27	1 yr.			11.1		
Zondek and Jacobowitz	1924	Berlin	1916–1922	117	?	?	19	1–7 yrs.	15.8	11.0	Rare		
Bund	1925	Marburg	1890–1914	76	62	12	39	up to 35 yrs.			10.0	41	20.0
Doederlein	1925	Munich	1910–1924	125	?	?	26	5 mos. 15 yrs.	4.0	38.6			
Greenhill	1926	Chicago	1917–1926	83	72	?	60	?			8.3	17	41.0
Neuwirth	1926	Wuerzburg	?	?	?	1	26				13.0		
Corwin and Herrick	1927	New York	1921–1926	56	48	0	44	6 mos. 6 yrs.	32.0	34.0		13	69.0
Nevermann	1927	Hamburg	1900	?	291	1	60	1–23 yrs.	13.3	5.0		33	21.0
Clow	1928	Boston	1905–1928	?	?	?	28	?	65.0				
Sym	1929	Edinburgh	1921–1926	?	?	3	74	3 yrs. plus			2.7	42	40.0
Peckham	1929	Baltimore	1919–1927	128	?	?	74	13 mos.			23.0	25	56.0
Schmechel	1929	Dresden	1915–1927	238	201	2						83	58.0
Seitz	1930	Frankfurt a. M.	1922–1929	104	94	0	78	2 mos.	0.0	0.0	0.0	0	
Kobes	1930	Kassel	?	?	?	?	32	3–85 mos.	15.6	9.4			
Mussey	1931	Rochester	?	10	7	0	7	?			28.6	2	50.0
Greifenstein	1931	Bonn	1912–1929	212	178	4	69	?		13.0		50	40.0
Hubing	1932	Frankfurt a. M.	1922–1930	117	102	?	32	3 mos. 7 yrs.	9.4	3.1		6	33.3
Rucker	1932	Richmond	1903–1930	206	173	10	64	3–28 yrs.	14.0			58	36.0
Breakey	1932	Sheffield	1908–1929	333	261	11	109	up to 20 yrs.	42.5	6.4			
Colavecchio and Prister	1932	Trieste	1925–1930	?	?	2	22	?	22.7	12.5			
Olsen	1933	Jylland	1910–1932	150	110	7	74 (102)	1–22 yrs.	17.6	1.2		74	16.3
Wagschal	1934	Frankfurt a. M.	1921–1932	142	131	?	27	1–7 plus yrs.	15.0	0.0		4	50.0

TABLE I.—SUMMARY OF THE LITERATURE DEALING WITH THE SEQUELAE OF ECLAMPSIA —Continued

Author	Year	Clinic	Period	Cases of eclampsia	Survivors	Remote deaths	Re-examined	Length of follow-up	Incidence of			Pregnant again	Recurrence of toxemia
									Hypertension	Proteinuria	Chronic nephritis		
									Per cent	Per cent	Per cent		Per cent
Kjelland-Mørdre	1935	Oslo	?	?								48	57.7
Effkemann	1935	Duesseldorf	1921–1935	120	?	?	62	1–14 yrs.	6.4	12.9		30	63.0
Tsuda	1936	Kyota	1923–1925	?	?	1	12	2 mos. 13 yrs.	16.7	25.0			
Mergner	1936	Leipzig	1921–1935	?	?	?						106	20.0
Seidentopf and Major	1936	Leipzig	1927–1932	?	?	?	16	28 mos. to 9 yrs.	50.0	31.2		7	28.4
Heinevetter	1937	Goettingen	?	?	?	?	39	2–6 yrs.	0.0	15.4		5	0.0
Bokelmann	1937	Berlin	1928–1934	?	120	?	10	11–96 mos.	20.0				
Teel and Reid	1937	Boston	1915–1935	168	122	8	80	1–21 yrs.	45.0	9.0		48	31.0
Peters	1937	New Haven	1922–1935	68	52	3	14	Up to 21 yrs.	78.0		43.0	18	94.5
Page and Cox	1938	Los Angeles	1927–1937	263	231	?	96	?	21.9			57	52.5
Tigges	1938	Cologne	1927–1935	?	193	?	45	?	13.6	15.5		23	21.7
Browne and Dodds	1939	London	1926–1938	48	45	0	40	6 mos. to 12 yrs.	30.5		0.0	5	80.0
Dieckmann and Brown	1939	Chicago	1932–1939	56	?	?						8	37.0

fetuses of less than 1000 grams be subtracted, the mortality would be 25.6 per cent.

Since there were 8 sets of twins, we have 177 babies to account for. Of these, 118 were discharged alive, 47 were stillborn, and 12 were neonatal deaths. The frequency distribution of the fetal weights and duration of pregnancy, with an analysis of the survival in each group, is summarized in Table II. As the pregnancy progresses and the fetus becomes larger, the rate of survival increases rapidly. Much of the adverse effect of eclampsia, upon the baby, would seem to lie in the premature delivery. Yet most of the deaths are not neonatal deaths, in which prematurity might be expected to be operative. The great majority, 79.6 per cent, of the babies lost are stillborn. Hence it seems that the older the fetus, the more resistant it is to whatever intra-uterine factor is so often lethal.

Extra-uterine existence costs fewer infant lives than does continued intra-uterine existence. This is true of all age groups, and for all weight groups except those below 2,000 grams. Of 144 babies born after thirty-fifth week, 28, or 19.4 per cent, were stillborn. Of the 116 born alive, 4, or 3.45 per cent, died. Assuming the death rate to remain constant, delivery at thirty-fifth week would have saved 23 infant lives, could the eclampsia have been foreseen.

In carrying a toxic patient to secure an older and heavier baby, with consequent lower neonatal mortality, we postulate that the babies be born alive. It is important, therefore, to learn what will be the effect of continuing maternal toxemia upon the baby still *in utero*. A dramatic answer to this question is given in Table III. When delivery is delayed more than 3 days after the first convulsion, 57.2 per cent of the fetuses die *in utero*. Delivery within 3 days shows a stillbirth rate of 25.8 per cent—less than half that seen in cases delivered later. In postpartum eclampsia, only 2.2 per cent are stillborn.

TABLE II.—FACTORS AFFECTING FETAL MORTALITY IN ECLAMPSIA. ANALYSIS BASED UPON 177 BABIES IN 169 ECLAMPSIA CASES

	Total cases		Discharged living		Still-births		Neonatal deaths	
	No.	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Age from menstrual history—in weeks								
Less than 32	20	11.4	1	5.0	13	65.0	6	30.0
33 to 34	9	5.1	2	22.2	5	55.6	2	22.2
35 to 36	16	9.1	8	50.0	8	50.0	0	
37 to 38	36	20.5	26	72.2	9	25.0	1	2.8
39 to 40	54	30.7	42	77.8	11	20.4	1	1.8
More than 40	38	21.5	36	94.8	0		2	5.2
Dates unknown	4	2.3	3	75.0	1	25.0	0	
Total	177	100.0	117	66.5	47	26.7	12	6.8
Weight in grams								
Less than 1,000	7	4.0	0		7	100.0	0	
1,001 to 1,500	13	7.5	1	7.7	9	69.2	3	23.1
1,501 to 2,000	14	7.9	7	50.0	2	14.3	5	35.7
2,001 to 2,500	19	10.8	14	73.6	4	21.0	1	5.4
2,501 to 3,000	23	12.5	16	69.6	6	26.1	1	4.3
3,001 to 3,500	41	23.0	38	92.7	3	7.3	0	
3,501 to 4,000	26	15.0	23	88.4	2	7.7	1	3.9
Greater than 4,001	9	5.2	7	77.8	1	11.1	1	11.1
Weight unknown	25	14.2	12	48.0	13	52.0	0	

Similarly, the duration of toxemia, regardless of time of convulsions, has a definite effect upon fetal survival, the death rate increasing as the toxemia is prolonged (Table III). In 29 patients carried for more than 4 weeks with toxemia, 62 per cent failed to get living babies, with an increase in both stillbirths (45 per cent) and neonatal deaths (31.3 per cent of live births). The duration of toxemia was not, however, the sole cause of increased mortality, since the degree of prematurity plays a rôle. We may use the fetal mortalities by weight groups for all eclampsia cases (Table II) to correct the mortality in the group of longer toxemia duration. This gives an expected fetal mortality of 49.2 per cent, as against the 62 per cent that actually occurred. The difference may be presumed to be attributable to the prolonged exposure to toxemia.

The fetal mortality increases as the toxemia becomes more severe. As Table III demonstrates, the mortality rate rises as the blood pressure or proteinuria increases. The relation between the number of convulsions and fetal death is nearly linear.

TABLE III.—THE EFFECT OF THE TOXEMIA UPON FETAL MORTALITY IN ECLAMPSIA

	Total cases		Discharged living		Stillbirths		Neonatal deaths	
	No.	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Average blood pressure								
Less than 140	37	21.1	32	86.5	4	10.8	1	2.7
141 to 180	83	46.9	62	74.6	15	18.2	6	7.2
Greater than 181	56	32.0	24	42.8	27	48.2	5	9.0
Proteinuria								
Less than 3 grams per liter	54	31.6	43	79.7	10	18.7	1	1.6
More than 3 grams per liter	115	68.4	70	60.9	34	29.6	11	9.5
Convulsions								
1	80	44.6	62	77.5	13	16.3	5	6.2
2	36	20.3	26	72.2	8	22.2	2	5.6
3	19	10.7	13	68.4	4	21.1	2	10.5
4 to 6	29	16.4	15	51.7	12	41.4	2	6.9
7 to 10	9	5.1	3	33.3	4	44.5	2	22.2
More than 11	5	2.8	2	40.0	3	60.0	0	
First convulsion to delivery								
More than 3 days	35	19.9	12	34.3	20	57.2	3	8.5
Less than 3 days	94	52.8	64	68.1	24	25.5	6	6.4
Postpartum eclampsia	48	27.3	46	95.7	1	2.2	1	2.1
Duration of toxemia								
Less than 3 days	20	16.9	17	85.0	3	15.0	0	
3 days to 1 week	21	17.8	15	71.5	6	28.5	0	
1 to 2 weeks	25	21.2	16	64.0	7	28.0	2	8.0
2 to 4 weeks	23	19.5	17	73.9	3	13.1	3	13.1
4 to 8 weeks	16	13.6	8	50.0	6	37.5	2	12.5
8 to 12 weeks	13	11.0	3	23.1	7	53.8	3	23.1

REMOTE MATERNAL MORTALITY

There have been 8 remote deaths. One of these, in a patient of 25 years, was caused by a septic abortion 18 months after the eclamptic pregnancy. Just before the abortion, the blood pressure was normal and the urine was free of protein. Two women of 17 and 26 years, respectively, died of pulmonary tuberculosis at 4½ months and 3½ years postpartum. Both had normal blood pressures, and one had had a subsequent normal pregnancy. (Two of our surviving patients have also been under treatment for tuberculosis.) An unusual in-

TABLE IV.—FOLLOW-UP STUDY OF ALL CASES OF ECLAMPSIA OCCURRING IN THE EXPERIENCE OF THE MARGARET HAGUE MATERNITY HOSPITAL

Year	Cases of eclampsia	Immediate deaths	Remote deaths	No follow-up	Re-examined in 1940*	Hypertensive (above 140/90)	Incidence of hypertension
1931–2	35	2		0	30	2 (4)†	15.08 per cent†
1933	18	1	1	1	15	4 (8)	(24.66 per cent†
1934	27	3	2	0	21	4 (5)	
1935	17	1	4	0	12	2 (4)	
1936	22	1		1	20	5 (7)	19.30 per cent†
1937	16	2	1	0	13	2 (3)	(28.90 per cent)†
1938	20	1	0	0	19	2 (3)	
1939	14	1	0	0	13	1 (3)	
Total	169	12	8	2	143	22 (37)	17.52 per cent† (27.28 per cent†
History of eclampsia			1		20	10	50 per cent

*An additional 4 patients, not seen in 1940, have had follow-ups of 10 months to 4 years. The last observation on these patients is included in the analysis.

†Based upon whole group of immediate survivors. Figures in parenthesis include as hypertensives those patients with either systolic or diastolic elevations. Relevant remote deaths included.

cidence of pulmonary tuberculosis in posteclamptic women has been noted by Rucker, and by Colavecchio and Prister; 1 of Bund's patients also died of this disease sometime after the toxemia.

The 5 remaining patients, 3.19 per cent of the eclampsia survivors, died of causes in the cardiovascular field. Of these, 3 were at the beginning of their fifth decade of life at the time of the eclamptic attack, and though their previous blood pressures were unknown, 1 had had diabetes for some time. Of the 2 others, one had known renal disease antedating the pregnancy, and the other had a perfectly normal course with many low blood pressure readings until the postmature onset of toxemia. These remote cardiovascular and renal deaths are as follows:

A. S., secundigravida, was 42 years of age at the time of her eclampsia which occurred in her first pregnancy for 14 years. Sudden death occurred 3½ years later, while she was at work in a factory. Hypertension had persisted since the eclampsia. Blood pressure never taken before the first convulsion. The cause of death assigned in the death certificate was coronary thrombosis.

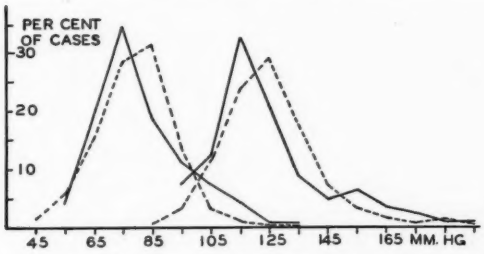

Fig. 1. The frequency distribution of diastolic and systolic blood pressures in women having had eclampsia (solid lines) and in control series (broken lines). Control series from literature has been corrected for the age distribution of the posteclamptics.

S. B., sextigravida, was 43 years of age at the time of admission in convulsion to the Margaret Hague Maternity Hospital. The patient died in Jersey City Medical Center 2½ years later of cardiac failure after a course of severe hypertension. Blood pressure before eclampsia was unknown.

A. E., quintigravida, aged 39 years, had eclampsia during delivery by midwife, and was admitted to the hospital. The patient had had diabetes for several years, but did not remember ever having had her blood pressure taken. After exactly 3 years, she was admitted to the Jersey City Medical Center with pneumonia. When about to go home cured, she suddenly died. The clinical diagnosis was cerebral thrombosis. Hypertension had persisted until death.

E. K., primigravida, aged 20 years, had a mild eclampsia at the Margaret Hague Maternity Hospital. The blood pressure had been normal until term. Seven months later she died in the Fitken Memorial Hospital. The postmortem diagnosis was acute glomerulonephritis and acute yellow atrophy of the liver.

R. T., septigravida (tertipara), aged 27 years, had had known renal disease for several years before her eclampsia in 1935. After delivery, the hypertension, gross proteinuria, hematuria, edema, and failing renal function persisted until uremic death 18 months postpartum.

Of the immediate survivors of eclampsia, then, only 8, or 5.1 per cent, have died in a 51 months average follow-up period. This stands in marked contrast with the figures of Herrick and Tillman who found that 22.5 per cent of the patients surviving eclampsia had died in the follow-up period (the length of the follow-up period was not specified for this group).

None of the remote deaths occurred in private patients; 3 had been clinic patients and 5 had been nonclinic, giving remote mortality rates of 3.8 and 14.3 per cent, respectively.

FOLLOW-UP FINDINGS

Hypertension. Table IV summarizes our material and sets forth the incidence of hypertension found in the recent re-examinations. Counting the 5 relevant remote deaths, the incidence of outright hypertension—blood pressure above 140/90—is 17.52 per cent. If we include as hypertensives those patients with elevated systolic pressure only, and those with increased diastolic pressure only, then the incidence becomes 27.28 per cent. The average incidence of hypertension for 1,454 posteclamptics, as summarized from 41 publications (Table I), is 19.88 per cent—"chronic nephritis" counted as hypertension.

The average blood pressure, at follow-up, in our patients is 124/81 millimeters of mercury (Table V).

TABLE V.—AVERAGE BLOOD PRESSURE

	Mean	Probable error	Standard deviation	Coefficient of variability
Systolic	124.04	1.12	19.76	15.94
Diastolic	80.9	0.878	15.50	19.15

The average age at follow-up is 29.75 years, for those with hypertension the average age is 34.30 years, and for those with normal blood pressure it is 28.50 years. For the patients who showed systolic elevations only, or diastolic elevation only the average age is 27.89 years. Perhaps some of these patients, when older, will be outright hypertensives, perhaps in others the residual lesions will heal, and they will be normal. For convenience, these will henceforth be called "half-hypertensive."

The average length of follow-up was 48 months for the patients having hypertension, and 52 months for those with normal blood pressure, the range for both groups is from 5 to 103 months (Margaret Hague Hospital series). In the series of women who had had eclampsia elsewhere, the average follow-up was 13 years, and ranges from 4 to 27 years.

The proportion of patients with increased blood pressure is slightly lower among those who had eclampsia before 1935 though the follow-up is, of course, longer. This difference is not statistically significant, for analysis by the chi^2 method reveals that there are 48.6 chances in 100 for the difference to arise by a sampling error alone. Since the incidence of hypertension in these two groups is similar, it might appear that posteclamptic hyperpiesia is manifested soon after the toxemia. It would then follow that re-examinations made many years after eclampsia are not especially advantageous in assessing the remote effects of the toxemia. In fact the interpretation of such long term follow-ups is complicated by the increasing incidence of hypertension in any group of older individuals. This factor of age may account for the higher incidence of hypertension which we have found in the 20 women who had had eclampsia in other hospitals. In this group, the average age at follow-up is 35.4 years; the incidence of hypertension is 50 per cent.

We have used 3 control series of women from the literature. Wetherby has made a study of the blood pressure distribution in 3,258 women visiting the out-patient clinic in Minneapolis; only cases of definite glomerulonephritis and aortic insufficiency were excluded. Blood pressures were taken with the patient sitting, after having waited for some time in the clinic. Of this series, 1,544 women were in the age groups represented by our patients at follow-up. The second control group is that of Alvarez and Zimmermann for 216 unmarried women, drawn from the office practice of Alvarez, in California. Blood pressures were taken with the subjects recumbent, after some rest, and either the lowest or the modal pressure of several readings was accepted.

The third control series is that of Saller, who analyzed the blood pressures of 1,743 women attending the out-patient clinic at Kiel; 99 per cent of these subjects were of the laboring class. Patients excluded from the analysis were those with recognizable renal disease, anemia, hormonal disturbances, and diabetes. Blood pressures were taken after the patients had waited at least half an hour in the clinic. Of Saller's series, 1,142 women were in the same age groups as our posteclamptics.

The age groups of these various control series were weighted so as to correspond with the age distribution in the posteclamptic

women, and the data of the three series were combined. The corrected frequency curves were then drawn in Figure 1, which also compares the blood pressures found in our posteclamptics. The 3 curves drawn from the published data of the authors cited are strikingly similar, for the systolic pressure and are very nearly parallel over the whole range of blood pressures observed. The diastolic curves are not in such good accord. These data, then, give a fair index of the frequency of increased blood pressure in a large group of women (2,902) who are living under diverse conditions.

As one compares the control curves with that for the posteclamptic women, it is apparent that there is a slightly increased incidence of hypertension among the patients who have had eclampsia. Of all the control series, Wetherby's shows the highest proportion of women with elevated blood pressures. Accordingly, this series has been taken for comparison in analyzing the statistical significance of the findings in the posteclamptics (Table VI).

TABLE VI.—CONTROL SERIES, CORRECTED FOR AGE

	Systolic greater than		Diastolic greater than	
	140 mm. Hg.	150 mm. Hg.	90 mm. Hg.	100 mm. Hg.
	Per cent	Per cent	Per cent	Per cent
Wetherby	14.84	8.25	20.7	5.1
Alvarez and Zimmermann	16.76	5.56		
Saller	6.89	2.67	6.51	1.1
Posteclamptics	18.0	13.1	23.4	13.1

It is only at pressures above 150 systolic and 100 diastolic that the posteclamptics show significantly higher incidences than do Wetherby's women.[1]

We may conclude, then, that there is an increased incidence of hypertension among posteclamptic patients; this difference is statistically significant.

Proteinuria. In 123 of the 159 patients, or 77.2 per cent, no protein was found in the urine. A very faint trace was detected in 32, or 20.2 per cent. As mentioned, the sulfosalicylic acid method was used. By the boiling and acetic acid test, the great majority of these urines would have been negative. Moreover, voided specimens were taken for the analysis. Short and Ley have recently demonstrated as much or more urinary protein in 20 to 31 per cent of nearly 5,000 women life insurance policy holders. We believe, therefore, that no significance can be attached to the minimal amounts of urinary protein in these 32 posteclamptic subjects.

One patient, with a normal blood pressure at 97 months after eclampsia and her last delivery, showed a trace of protein in a voided specimen. Another, A. E., whose case is described under the remote deaths, had a 2 plus (about 3 grams per liter) proteinuria. The third patient to have a proteinuria of significant degree is described under the remote deaths (R. T.). She ran 8 to 10 grams per liter of protein until going into terminal uremia; she was the only patient to show urinary casts in significant numbers. In this case, renal disease was known to have antedated the eclamptic pregnancy.

In summary, only 3 patients had proteinuria of possibly significant degree. One of these was a chronic nephritic before her pregnancy, and one was probably a chronic hypertensive before eclampsia.

Urea clearance. Urea clearances were done in 131 cases at follow-up. An additional 21 patients attained urinary specific gravities higher than 1.025 in casual urines; since protein and sugar were absent, urea clearances were not done because they would have been normal.

In only 5 cases was the clearance found to be less than 60 per cent, and therefore subnormal. In 2 of these, hypertension without proteinuria was also found. One patient was the remote nephritic death (R. T.). In the 2 others, the lowered urea clearance was the only positive finding, and perhaps repetition of the test would give normal readings. In

[1] Dividing each of the series at these pressures, constructing four-fold tables, and solving for chi^2 in order to get the probabilities, we find that there really is a significant difference in the control and posteclamptic groups. There are only 4 chances in 100 that the difference between Wetherby's corrected curve and the curve for the posteclamptics could arise by sampling error—considering the portion beyond 150 millimeters of mercury for the systolic pressure. For the curves beyond diastolic pressures of 100 millimeters of mercury, there are but 63 chances in 100,000 that sampling errors could give the difference.

any normal subject, the urea clearance does occasionally fall below 60 per cent in the wide variations which may be observed.

The average clearance is somewhat lowered, both in patients with normal blood pressure and in the hypertensives (Table VII). Possibly the average would have been closer to the ideal 100 per cent if clearances had been done on the patients with high urinary specific gravities, for with their omission there is a factor of selection.

TABLE VII.—UREA CLEARANCE

	Cases	Mean, as per cent of average normal	Standard deviation
Patients with: Normal blood pressure	95	88.2	16.86
Hypertension	36	89.1	21.83

Blood chemistry. For want of space, we shall merely say that the blood levels of nonprotein nitrogen, urea nitrogen, and uric acid were always found to be within normal limits except in the case of the remote nephritic death (R. T.).

The blood sugar was pathologically increased in 3 cases. In 2 of these, blood sugars were normal at the time of the eclampsia and in the puerperium. Diabetes had become manifest in the interim.

Physical examination. Of the 38 hypertensive patients seen at follow up, 19 had cardiac enlargement either by physical signs or by x-ray examination. Of these, 2 cases were associated with rheumatic heart disease. Eight of the patients had signs and symptoms of cardiac insufficiency. One was admitted to the hospital during the course of the follow-up, in cardiac failure, with the diagnosis of hypertensive cardiovascular disease.

Special interest was attached to the eyeground findings since their importance has been emphasized by Corwin and Herrick and by others as substantiating the nature of the hypertension following toxemia. Of the 38 hypertensive patients, 26 had satisfactory eyeground examinations. Four had died with no record of fundus readings, 3 were not examined because they were seen in the home, and in 2 the pupils were too contracted for satisfactory examination. Since the patients were unaccompanied to the clinic, in many cases, dilatation of the pupils was omitted.

Of the 26 examined, 23 had definite eyeground changes. In 19 this consisted of attenuation of the arterioles with or without irregularity of the lumen. In 4 irregularity of the arteriolar lumen was noted, although the arterioles in general were of average caliber as compared with the veins. In 9 patients compression of the vein at the arteriolar crossing was noted. The light reflex was so increased in 9 patients as to excite a special note. In 2 the wall of the attenuated artery looked unusually heavy, with the lumen reduced to a thready line. In 1 patient, hospitalized in cardiac failure, edema of the discs appeared and in another "albuminuric retinitis" with exudate and hemorrhage was seen. Marked choroidal change was present in 2 instances.

The findings in the "half-hypertensive" group of 11 patients confirmed our impression that these included a high percentage of cases which would become outright hypertensive cases on later examination, Of the 8 patients investigated for fundus changes, 4 showed abnormalities; 2 had irregularity of the arteriolar lumen and 2 general attenuation of the arterioles.

Among the patients with normal blood pressure, there were 4 instances of significant eyeground changes. Two had thickening of the arteriolar walls, increased light reflex, but no irregularity in caliber. Two showed irregularity of the arterioles without change in the general caliber of the vessels.

The radial arteries were palpated in each case, but it was not felt that any information about the state of the vascular system was obtainable in this way which could not be more reliably ascertained by other means.

In 7 patients still surviving, the full blown picture of high blood pressure, radial artery sclerosis, eyeground changes, and cardiac enlargement was present.

FACTORS AFFECTING THE PERSISTENCE OF HYPERTENSION

In analyzing the elements which seem to contribute to the persistence of hypertension, we find that some are amenable to control,

some can be modified in part, while others cannot be affected.

Antecedent hypertension or renal disease. The prepregnancy history of most of our patients is not accurately known, but so far as the reliable cases go, we confirm Teel and Reid. Some posteclamptic hypertensive patients had hypertension before the pregnancy; and in 24 women who were known to be normal before the twenty-fourth week of pregnancy, none is an outright hypertensive now, though one-sixth of them do show either an elevated systolic or an elevated diastolic pressure (Table VIII).

TABLE VIII.—PREGNANCY HISTORY

	Normal before 24th week	Hypertension before pregnancy	History unknown
No. cases	24	6	135
Now hypertensive	0	100%	20.9%
Half-hypertensive	16.67%	0	10.4%
Normal	83.3%	0	68.7%

Since there are so few patients in whom prepregnancy blood pressures were available, we have made a further analysis on the basis of the first observed blood pressure, when that reading was made 4 weeks or more from term. The first reading, in the clinic, is very frequently higher than those subsequently observed, before the onset of the toxemia. In general, the lower the first observed blood pressure, even in the normal range, in late pregnancy, the less likely the eclamptic patient is to have hypertension in the follow-up.

TABLE IX.—RELATIONSHIP OF BLOOD PRESSURE TO INCIDENCE OF HYPERTENSION

First blood pressure	Less than 120	121–140	More than 140
	Per cent	Per cent	Per cent
Incidence of hypertension in follow-up	6.5	32.0	43.8
Half-hypertension	10.8	0	6.2
Normal	82.7	68.0	50.0

Age when eclamptic. The older the patient at the time of eclampsia the more probable hypertension is to be found at follow-up (Table X).

TABLE X.—RELATION OF AGE TO ECLAMPSIA AND HYPERTENSION

Age in years	15–20	21–25	26–30	31–36	Over 36
No. cases	48	57	28	26	13
Hypertension, per cent	10.45	17.58	17.84	30.65	69.3
Half-hypertension, per cent	12.50	7.02	14.28	11.55	7.7
Normal, per cent	77.05	75.40	67.88	57.80	23.0

As Teel and Reid suggested, this higher incidence of persistent hypertension among the older eclamptics may mean merely that more of them had high blood pressure before the pregnancy. Perhaps, too, the younger vascular systems are more resistant, or have a greater reserve which must be vitiated before hypertension appears.

Age at follow-up. Since, in the population as a whole, the incidence of hypertension rises with age, it is not surprising to find a similar trend in the posteclamptics. However, if the "half-hypertensives" be considered as hypertensive, the picture is confused and no regular trend can be discerned.

TABLE XI.—AGE AT FOLLOW-UP

Age in years	15–20	21–25	26–30	31–35	36–40	Over 41
No. cases	10	39	55	24	28	17
Per cent hypertension	0	7.9	18.9	17.4	32.2	58.8
Per cent half-hypertension	30.0	5.3	15.1	8.7	7.1	11.8
Per cent normal	70.0	86.7	66.0	73.9	60.7	29.4
Controls: Per cent hypertension in Alvarez series			12.0	27.4		36.2
Per cent hypertension in Wetherby's series	8.0	9.0		19.0		42
Per cent hypertension in Saller's series	1.78	3.71		6.95		30.41

Considering only the outright hypertensives, it is seen that all age groups of posteclamptics, except the first, show more than the expected incidence of blood pressures above 140/90. Comparing the relative effects of "age when eclamptic" and "age at follow-up," it would appear that "age when eclamptic" bore the more consistent relation to subsequent hypertension.

Parity. As previous writers—Peckham, Seidentopf and Major, Jensen—have demon-

strated, the incidence of posteclamptic hypertension increases with the parity of the patients.

TABLE XII.—PARITY

Para	I	II	III	IV and more
No. cases	60	51	29	34
Per cent hypertension	6.8	14.0	39.3	47.0
Per cent half-hypertension	8.5	8.0	3.5	5.9
Per cent normal	84.7	78.0	57.2	47.1

Since, in general, the patients of higher parity are older, we have tried to separate the factors of age and number of births, though there are not enough cases to give clear-cut results in all age groups. The analysis, shown in Table XIII, indicates that parity, independently of age, seems to be a governing factor in the persistence of hypertension. However, this may in turn be explained by the occurrence of other toxemias in some of the pregnancies.

Time of onset and duration of toxemia. As has been pointed out in the introduction, two factors—time of onset and duration of toxemia—have not been hitherto separated in analyzing their influence upon the finding of hypertension at follow-up examination. It is especially important to make this differentiation because it has a self-evident bearing upon the treatment of antepartum eclampsia.

TABLE XIII.—RELATION OF PARITY, INDEPENDENTLY OF AGE, TO SUBSEQUENT HYPERTENSION AFTER ECLAMPSIA

Status at follow-up		Cases	Hypertensive	Half-hypertensive	Normal
Age	Parity	No.	Per cent	Per cent	Per cent
21–25	I	21	9.5	4.8	85.7
	II	12	16.7	16.6	66.7
26–30	I	20	0.0	10.0	90.0
	II	17	5.9	0.0	94.1
	III	9	22.2	0.0	77.8
	IV+	8	37.5	0.0	62.5
31–40	I	12	16.7	8.3	75.0
	II	15	20.0	0.0	80.0
	III	14	50.0	0.0	50.0
	IV+	14	35.7	7.2	57.1
41+	I, II, III, IV	7	42.8	28.6	28.6
	V and more	10	80.0	10.0	10.0

In 1878, Schroeder suggested that the longer a patient was carried with toxemia, the more likely she was to have a "chronic nephritis" later. Perhaps the first to publish quantitative studies on the question was Gibberd. He found that in 38 previously normal women, in whom pregnancy was terminated within 3 weeks after the appearance of toxemia, only 5 per cent developed "chronic nephritis." Among 29 previously healthy patients in whom the toxemia was allowed to continue for more than 3 weeks, 28 per cent developed signs of "chronic nephritis." The recurrence rates of toxemia in subsequent pregnancies were 36 and 76 per cent, respectively. Disregarding the fact—as Gibberd did—that patients carried for longer periods must often have earlier onsets of toxemia, it seems logical to consider that exposure of the vascular system, including the blood vessels of the kidney, to continuing toxemia may cause progressive damage. The hypertension found at follow-up, then might be said to be caused by the toxemia.

When toxemia onset is considered without regard to its duration, early appearance seems to be associated with an increased incidence of hypertension at follow-up. Disregarding the duration of toxemia, the gross incidences of

TABLE XIV.—ELEVATED BLOOD PRESSURE AT RE-EXAMINATION

Toxemia onset	Follow-up findings		
	Hypertension Per cent	Half-hypertension Per cent	Normal Per cent
Before seventh month	44.4	5.6	50.0
Seventh to eighth month	20.0	20.0	60.0
Eighth to ninth month	10.6	13.6	75.8

TABLE XV.—DURATION OF TOXEMIA

Duration of toxemia	Follow-up findings		
	Hypertension Per cent	Half-hypertension Per cent	Normal Per cent
Less than 3 weeks	9.3	13.3	77.4
More than 3 weeks	45.7	12.6	41.7

TABLE XVI.—RELATION OF DURATION OF TOXEMIA TO SUBSEQUENT HYPERTENSION

Findings at follow-up	Onset of toxemia					
	Before 7th month		7th–8th month		8th–9th month	
	Carried with toxemia					
	Less than 3 weeks	More than 3 weeks	Less than 3 weeks	More than 3 weeks	Less than 3 weeks	More than 3 weeks
	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent
Hypertension	14.3	63.6	0.0	60.0	10.3	12.5
Half hypertension	14.3	0.0	20.0	20.0	12.0	25.0
Normal	71.4	36.4	80.0	20.0	77.7	62.5

elevated blood pressure at the re-examination are shown in Table XIV. Similarly when the duration is considered alone, an increased incidence of hypertension parallels longer duration (Table XV).

However, when we examine in each case the effect of onset in terms of the duration of the toxemia, as in Table XVI, it is seen that the important factor of the two is duration of the toxemia; the time of onset, *per se*, does not significantly affect the remote prognosis. When the toxemia appeared in the seventh month, a high proportion of patients were carried for several weeks before delivery, in the interests of the fetus. This longer average duration of toxemia masks the fact that a patient having toxemia appearing in the seventh month—if promptly delivered—is no more likely to have permanent hypertension than is the woman who has toxemia appearing at term.

Severity of toxemia. Our data accord with what several previous writers have pointed out; a definite correlation can be drawn between the severity of the eclampsia and the incidence of subsequent hypertension. When the systolic blood pressure, in eclampsia, averages less than 180 milligrams of mercury, 10.66 per cent of the patients had hypertension at follow-up. The level of blood pressure and degree of proteinuria, below this point, do not seem to influence the appearance of persistent hypertension. In those cases in which the systolic blood pressure, during eclampsia, averages more than 180, the incidence of persistent hypertension jumped to 44.8 per cent (Table XVII).

TABLE XVII

	Blood pressure less than 150		Blood pressure 151–180		Blood pressure 181–200		Blood pressure more than 200	
	Proteinuria	Proteinuria	Proteinuria	Proteinuria	Proteinuria	Proteinuria	Proteinuria	Proteinuria
	<2+	>2+	<2+	>2+	<2+	>2+	<2+	>2+
No. cases	23	24	17	58	2	19	1	7
Per cent hypertensive	13.05	16.67	5.89	8.62	0	47.4	100	42.9
Per cent half-hypertensive	4.35	8.33	5.89	12.07	0	15.8	0	28.6
Per cent normal	82.60	75.00	88.22	79.31	100	36.8	0	28.6

Blood pressure and proteinuria at 10 days and 6 weeks postpartum. Future hypertension cannot be predicted with any confidence from the blood pressure and urinary protein findings at 10 days or at 6 weeks after delivery. However, patients who have not returned to normal within this period are considerably more liable to subsequent hypertension (Table XVIII).

TABLE XVIII

	No. cases	Hypertension in follow-up Per cent
Blood pressure normal at 10 days	99	13.13
Blood pressure high at 10 days	58	37.92
Blood pressure high at 6 weeks	15	46.70
Proteinuria less than 2 grams per liter at 10 days	107	11.22
Proteinuria more than 2 grams per liter at 10 days	41	46.30

Weight/height ratio at follow-up. Hypertension generally is more common in individuals who have high weight/height ratios, i.e. in the obese. The incidence of hypertension in our posteclamptics shows this same relation to obesity (Table XIX).

TABLE XIX.—WEIGHT/HEIGHT RATIO

Weight/height ratio	No. cases	Hypertension Per cent	Half-hypertension Per cent	Normal Per cent
Less than 1.80	22	4.5	0	95.5
1.81–2.60	77	13.0	7.8	79.2
More than 2.61	23	30.4	26.1	43.5

TABLE XX.—RELATION OF SUBSEQUENT PREGNANCIES TO THE INCIDENCE OF POSTECLAMPTIC HYPERTENSION

Subsequent pregnancies	Cases	Status at follow-up					
		Hypertensive		Half-hypertensive		Normal	
		Cases	Per cent	Cases	Per cent	Cases	Per cent
None	92	19	20.5	7	7.6	66	71.8
One	48	7	14.6	5	10.4	36	75.0
Normal	31	2	6.5	2	6.5	27	87.0
Toxic	17	5	29.4	3	17.7	9	52.8
Two	22	8	36.4	2	9.1	12	54.5
Both normal	12	1	8.3	2	16.7	9	75.0
One normal One toxic	6	3	50.0	0		3	50.0
Both toxic	5	4	80.0	0		1	20.0
Three	10	4	40.0	0		6	60.0
Four	4	3	75.0	0		1	25.0

Since weight reduction in overweight patients will often reduce the blood pressure (Ley), it would therefore seem that the control of obesity might be of value in posteclamptic patients.

Subsequent pregnancies. One of the most practical questions arising for the remote prognosis in a patient who has had eclampsia is that of further pregnancies. We have seen many posteclamptic patients in whom no abnormality can be found, and who have been warned against any further pregnancy; in a few cases, therapeutic abortions have been done (elsewhere) because of the eclamptic history alone. Many publications lend support to these steps.

We have made an analysis of the 84 posteclamptic patients who have had subsequent pregnancies, and compared them with the 92 patients who have had no later pregnancy.

From the data in Table XX, it appears that one or two subsequent *normal* pregnancies will not affect adversely the remote prognosis. A subsequent toxic pregnancy, however, will increase markedly the chances for a persistent hypertension.

It is interesting to note that if one subsequent pregnancy occurs, and if it is toxic, the incidence of hypertension at follow-up is about 50 per cent. When 2 subsequent pregnancies occur, 1 normal and 1 toxic, the normal pregnancy does not seem to count, and the toxic pregnancy exerts its same effect—the incidence of hypertension is again found to be about 50 per cent.

We have made an analysis of the effect of all pregnancies, before and after eclampsia. Since the incidence of hypertension is lowest among patients who have had only the one (eclamptic) pregnancy, and almost equally low among those whose other pregnancies have been normal, it seems that *perhaps the most important single factor in determining future hypertension is another toxemia* (Table XXI).

TABLE XXI

Follow-up finding	No other pregnancy	Other pregnancies normal	Other toxemia uncertain	Other toxemia	
				Nonconvulsive	Eclampsia
No. cases	58	45	13	47	8
Per cent hypertension	6.89	8.90	30.8	44.7	62.5
Per cent half-hypertension	8.62	0.0	7.7	13.0	0.0
Per cent normal	84.49	91.10	61.5	42.3	37.5

The incidence of hypertension is so low in posteclamptic patients who have had no other toxemia, that we may question whether eclampsia alone does cause remote hyperpiesia. Taking the data at face value, it might seem that eclampsia merely predisposes the patient to toxemia which in turn causes the hypertension found at follow-up. Of the 38 posteclamptic hypertensive patients, 26, or 68.4 per cent, are known to have had at least one other toxic pregnancy; 8, or 21 per cent, are known not to have had another toxemia, and in 4 cases this is uncertain.

RECURRENCE OF TOXEMIA

Of all the posteclamptics, 90 patients have had 143 subsequent pregnancies; 26, or 18.17 per cent, of these terminated in abortions; 16, or 11.18 per cent, in stillbirths; and 101, or 70.65 per cent, in live births. Thus the fetal losses in later pregnancies almost exactly match those present in the eclamptic pregnancy group.

Thirty-seven of the 84 patients carrying their pregnancies past the twenty-fourth week had 55 toxemias, or 47 per cent, of which 2, or 2.38 per cent, were again eclamptic. The published data from Table I show 881 women pregnant after eclampsia, with a toxemia recurrence of 39.3 per cent. However, many of these papers do not include mild toxemias, but only count recurrent eclampsia and severe toxemia.

Prenatal care did not seem to avail much in reducing the rate of *recurrence* in toxemia, though the incidence of severe toxemia is probably diminished by such care (Table XXII).

TABLE XXII.—PRENATAL CARE

	No care	Private care	Clinic care	
			Less than 2 mo.	More than 2 mo.
Pregnancies	11	31	28	46
Toxic, per cent	54.5	48.4	53.5	41.3

The age of the patient at the time of eclampsia is directly related to the recurrence of toxemia in subsequent pregnancies (Table XXIII).

TABLE XXIII.—AGE WHEN ECLAMPTIC

	15–20	21–25	26–30	31–35	36–40
Recurrence of toxemia, per cent	37.15	41.95	55.60	71.50	100

The severity of the eclampsia affects the recurrence rate of toxemia in later pregnancies (Table XXIV).

TABLE XXIV

	Average blood pressure in eclampsia			
	Less than 150 mm.	151–180	181–200	More than 201
Pregnant again	29	27	8	2
Toxic in later pregnancy, per cent	20.7	48.1	62.5	100

We cannot assess the influence of time of onset and duration of toxemia independently, because we have too few cases in which the necessary data are known. However, in 66 cases (51 patients) we do know the duration of toxemia in the eclamptic pregnancy. As shown in the analysis, any patient carried with toxemia for more than 2 weeks is more likely to suffer later toxemia (Table XXV).

TABLE XXV

Duration of toxemia in eclamptic pregnancy	Subsequent pregnancies	Toxemias, per cent
Less than 2 weeks	39	20.5
More than 2 weeks	27	63.0

Subsequent pregnancy, to restate an idea current in the literature, is a delicate test of the damage left by a toxemia. While the severity of the eclampsia does affect the remote incidence of persistent hypertension, the effect is more clearly seen in the recurrence rate of toxemia. Similarly, duration of toxemia affects the later appearance of hypertension; but toxemia of even shorter duration has an equally marked effect upon the recurrence of toxemia.

It is a common practice to warn posteclamptic patients against having another pregnancy "too soon." This serves to cut down the total number of pregnancies, which is beneficial as we have seen above. This recommendation also carries the implication that after eclampsia the damage inflicted may heal gradually. On the basis of the few cases available we have sought for a relationship between the interval from eclampsia to conception and the recurrence of toxemia. There seems to be a rough trend to indicate that the longer the interval, the less the chance of having a recurrent toxemia (Table XXVI).

TABLE XXVI

	Interval from eclampsia to conception					
	Less than 3 months	3–6 months	7–12 months	13–24 months	25–36 months	More than 37 months
No. pregnant again	4	7	14	18	16	14
Per cent toxic in first pregnancy after eclampsia	25.0	71.5	64.2	55.7	31.2	50.0

SUMMARY AND CONCLUSIONS

The immediate maternal mortality, in a series of 169 cases of eclampsia, was 7.10 per cent, uncorrected.

The fetal losses, including all cases, were 33.5 per cent. The chief source of fetal loss is stillbirth. The factors contributing to the death rate are prematurity, and duration and severity of the maternal toxemia.

An analysis is presented of the eclamptic pregnancies, as a basis for an assessment of the effects of various factors in pregnancy upon the persistence of hypertension.

Of the 155 women surviving eclampsia, 8 have died subsequently; 5 deaths were in the field of cardiovascular and renal disease.

The incidence of hypertension at follow-up, in the Margaret Hague Maternity Hospital series, was 17.5 per cent; in the women who had had eclampsia elsewhere, it was 50 per cent. An additional 9.8 per cent of the former had a systolic or a diastolic elevation alone.

The incidence of hypertension among the posteclamptic patients is significantly greater than in the female population at large, correction being made for age distributions.

The incidence of proteinuria of significant degree is 2.6 per cent at follow-up.

Renal function, as measured by the urea clearance and urinary specific gravity, is in the normal range in at least 97 per cent of the patients at follow-up.

The majority of the living hypertensives had significant eyeground findings. Half had cardiac enlargement, and 8 had signs and symptoms of cardiac insufficiency.

An extensive analysis has been made of the factors contributing to the persistence of hypertension. In general, we may say that high blood pressure is more likely to be found at follow-up if there is antecedent renal or vascular disease. Also the higher the first observed blood pressure in pregnancy—even in the normal range—or the older the patient when eclamptic or at follow-up, or the more children she has had, or the longer she is carried with toxemia, or the more severe the eclampsia, or the more obese the patient, the more likely hyperpiesia is to persist. The time of onset of toxemia, whether in the seventh month or at term, has no direct effect upon the remote prognosis; early onset often seems to favor future hypertension only because the patients are carried for considerable periods before delivery.

None of the above considerations is so decisive in conditioning remote hypertension as is recurring toxemia subsequent to the eclampsia. Hypertension is not often found in a woman who has had a single eclampsia as the only toxemia of pregnancy. Most of the posteclamptic hypertensives have had another toxemic pregnancy.

The recurrence rate of toxemia in pregnancies after eclampsia was found to be 47 per cent. In general, the factors enumerated above which favor the persistence of hypertension favor in even greater degree the recurrence of toxemia.

After the thirty-fifth week of gestation, the fetus fares much better *ex utero*, in eclampsia.

In subsequent pregnancies after eclampsia the fetal losses were 29.4 per cent.

Advising against future pregnancies in a posteclamptic would seem to be justified by the recurrence of toxemia in 47 per cent of cases, with a consequent 8 fold increase in chances for permanent hypertension if the pregnancy is toxic.

In evaluating a given patient's risks in a future pregnancy, one may consider the present blood pressure, the severity of the past eclampsia, duration of that toxemia, obesity, age, and interval since the eclamptic pregnancy.

We wish to express our grateful appreciation to Dr. S. A. Cosgrove for his painstaking criticism of this paper. Drs. J. F. Norton and E. G. Waters have also made helpful suggestions. We are indebted to many physicians who have permitted us to re-examine their private patients, and to the many people who have co-operated in finding lost patients. Many of the blood and urine urea examinations were done by Frances Orsato and Peter Marotta. Mrs. E. R. Chesley assisted in finding and examining patients.

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A STUDY OF THE CLINICAL MANIFESTATIONS AND THE RESULTS OF TREATMENT OF TWENTY-TWO PATIENTS WITH RAYNAUD'S SYMPTOMS

CARL A. JOHNSON, M.D., Chicago, Illinois

THE symptom complex commonly known as Raynaud's disease has received an unusual amount of attention in medical literature since its original classical description by Raynaud in 1862 (7, 8). Little has been added to the original description or theories, however, and Lewis (6) states that, "just as Raynaud's description stands, so his views of the malady predominate today."

It was recognized early that what is known as Raynaud's disease is probably not a disease but a symptom complex, the objective manifestations of which have a multiple etiology. John Hunt, in his recent review of the subject, stated, "nearly fifty years ago Hutchinson recognized clearly the true significance of Raynaud's thesis, and in his writings he stressed the fact that, "Raynaud's phenomenon," as he called it, was not a clinical entity at all but a syndrome occurring in many different conditions." Hunt subscribes to this view, but believes that the term Raynaud's disease is so well established it will continue to be used whether it has any meaning or not.

One is impressed with the wide difference of opinion regarding the nature and etiology of Raynaud's symptoms, the diagnosis, and whether what is known as Raynaud's disease even exists as a clinical entity. Allen and Brown, reviewing Raynaud's 26 original cases, concluded that only 6 could be classified as having Raynaud's disease. Hunt, reviewing the same cases, concluded that only 1 of the series had Raynaud's disease, and this one was doubtful. He stated that even if Raynaud's disease exists, it must be rare.

A wide difference of opinion exists regarding the nature and cause of the vascular phenomena observed in Raynaud's attacks. Raynaud thought the spasms were due to an abnormal vasomotor tone. Lewis thinks the attacks are due to a "local fault" with normal vasomotor tone.

This confusion and difference of opinion is reflected in the modes of treatment. Persons subscribing to abnormal vasomotor tone advocate operations on the sympathetic nervous system; those thinking the spasms due to a local fault use general measures in an attempt to avoid attacks and to correct the local fault.

From the Department of Medicine, Northwestern University.

Realizing the controversial nature of all aspects of the subject, it is with hesitation that I add another report which offers no solution. But this report is believed to be justified by its presentation of a new method of attack, some new ideas on the state of the vascular system, and the results of medical as contrasted with surgical management. This study involves the history, physical findings, laboratory findings, treatment, and course of 22 patients with Raynaud's symptoms in the hands, or in the hands and feet. Raynaud's symptoms never occurred in the feet alone.

To conserve space and illustrations, the detail concerned with the patients is summarized in tables. Table I is a summary of the patients' histories. Although self-explanatory, a few findings require some comment. There are two colored patients in this series: one male and one female. No reports of Raynaud's disease in the colored race could be found.

In this series, all the patients had Raynaud's symptoms in the fingers, 11 had similar symptoms in the toes, but in no case did the symptoms occur in the toes without the patient being subject to the symptoms also in the fingers. In only one of the patients with Raynaud's symptoms in the toes were the symptoms severe enough to require any particular care. A lumbar sympathectomy was done on this patient; the results are reported in detail in the case report of Mr. Y.

Emotional spells as a cause of Raynaud's symptoms are worthy of comment. In only 3 of the patients were they a frequent cause and in these 3 sympathetic surgery failed to produce any improvement as judged by recurrence of symptoms and the frequency and severity of attacks.

Table II is a summary of the laboratory findings and associated diseases. Associated diseases are comparatively common in this series: 2 had syphilis; 13, a mild secondary anemia; 2, a severe anemia; 3, stiffness of the finger joints, scleroderma, ulcers, loss of tissue, and loss of fingernails; and, 2 had sclerodactylia. It is very interesting to note that the scleroderma, stiffness of

TABLE I.—SUMMARY OF HISTORICAL FINDINGS

	No. of cases
Sex	
Females	18
Males	4
Race	
White	20
Colored	2
Age at onset	
1–10 years	1
10–20 years	2
20–30 years	5
30–40 years	7
40–50 years	6
50–60 years	1
Site of Raynaud's symptoms	
Fingers	22
Fingers and toes	11
Toes, not fingers	0
Severity of symptoms—in hands	
Mild	9
Severe	13
in feet	
Mild	10
Severe	1
Noted in family history	3
Symptoms	
Local pallor	22
followed by	
Local cyanosis	17
followed by	
Local rubor	22
Attacks caused by	
Cool air, most easily	22
Cool water, less easily	22
Chilling of body by cold drinks	7
Emotional spells	
occasionally	6
frequently	3
Attacks relieved by	
Immersion of hands in warm water	16
Immersion of hands in cold water followed by warm	1
Shaking of hands	2
Rubbing of hands	5
Warm air	3
Influence of seasons	
Worse in winter (4+)	22
Mildly cold (2–4+)	22
Present in summer (1+)	16
Presence of associated findings—two or more of following:	
Loss of fingernails	3
Loss of tips of fingers	5
Scleroderma	5
Sclerodactylia	3

TABLE II.—SUMMARY OF LABORATORY EXAMINATION

	Cases
Red blood count	
3.0 to 3.5 million	1
3.5 to 4.0 million	5
4.0 to 4.5 million	8
4.5 to 5.0 million	4
5.0 to 5.5 million	3
Hemoglobin—%	
55 to 59	2
60 to 64	0
65 to 69	2
70 to 74	6
75 to 79	5
80 to 84	2
85 to 89	1
90 to 94	0
95 to 99	3
White blood count	
2000 to 3000	1
3000 to 4000	2
5000 to 6000	4
6000 to 7000	4
7000 to 8000	5
8000 to 9000	4
Sedimentation rate (mm. per hour)	
1 to 12	9
12 to 18	6
18 to 24	1
24 to 30	1
Wassermann and Kahn	
Negative	20
Positive	2
Electrocardiograms	
No significant changes	19
Evidence of myocardial damage	3
Basal metabolic rate:	
Within normal limits	9
Minus rate	2
Roentgenograms of hands	
No bone changes	17
Changes in terminal phalanges	2
Sclerodactylia	3
Peripheral circulation	
Functional occlusion only	10
Organic occlusion	
1 plus	5
2 plus	3
3 plus	4
Associated trophic disturbances	
Loss of fingernails	4
Ulcers	5
Loss of tissue	5
Scleroderma	
1 plus	1
2 plus	3
3 plus	1

the joints, ulcers, loss of tissue, loss of fingernails, and sclerodactylia occurred in patients with the most organic vascular pathology as determined by plethysmographic studies. The manner of making these studies has been presented in a previous article (3), but illustrative records will be shown in case reports to follow.

TREATMENT

The treatment of patients with Raynaud's symptoms may be classified as follows: (1) the relief of mental anxiety, (2) the improvement of an anemia, (3) the treatment of any specific disease, (4) surgical treatment by operations on the sympathetic nervous system.

The relief of mental anxiety. Case 4 is a striking example. Previous to the onset of the Raynaud's symptoms in December, 1936, the patient had been told that she had diabetes. She continued

on a diet until she was admitted to St. Luke's Hospital Out Patient Dispensary for care in October, 1937. A thorough examination revealed no evidence of diabetes. About one week after the patient had been reassured she did not have diabetes the Raynaud's symptoms disappeared. Dr. Joseph L. Miller communicated to the author the incident of a patient in whom the Raynaud's symptoms disappeared following an auto accident. It is possible the marked emotional change in these patients was sufficient to effect a cure.

The improvement of an anemia. This is well illustrated by the following report:

Mrs. L. A., a white female, aged 45 years, first came under observation November 18, 1936, with complaints of typical severe Raynaud's symptoms in the first three fingers of both hands, and similar attacks in the large toes of both feet. The attacks first appeared 3 years previously in the winter and during the cold weather were so severe that she was virtually confined indoors. The symptoms were absent in the summer. She gave a history of severe uterine bleeding during and between menstrual periods. She had been advised to have this treated, but had refused because of fear of an operation. A blood count revealed the red blood cells as 3,910,000 and the hemoglobin as 45 per cent. She still refused surgery, but following intensive liver and iron therapy her blood count improved to within normal limits and as long as maintained she remained virtually free from Raynaud's symptoms even in the winter. She had only one or two attacks per month as compared to several a day before treatment. In the spring of 1939, following a hysterectomy her blood count rose further. On February 22, 1940, her red blood cell count was 5,350,000 and her hemoglobin 115 per cent. She remained free from Raynaud's symptoms the following winter.

Several patients in this series had a similar, but possibly not so striking, improvement as this.

The treatment of an underlying specific disease. The following illustrates what may be accomplished if the cause of the Raynaud's symptoms can be found.

The patient had severe Raynaud's symptoms since 1932 with associated ulcers, loss of tissue, loss of fingernails, stiff joints of the fingers, scleroderma and sclerodactylia. In 1934 she was subjected to a bilateral removal of the stellate and second dorsal sympathetic ganglia, with very transient improvement. The symptoms gradually became worse. In June, 1935 antiluetic treatment was instituted. From then on she had complete relief from the Raynaud's symptoms through five winter seasons. Although the Raynaud's symptoms have been relieved completely, she has occasional ulcers on her fingers. Records taken from this patient following surgery are illustrated in Figures 6, 7, and 8.

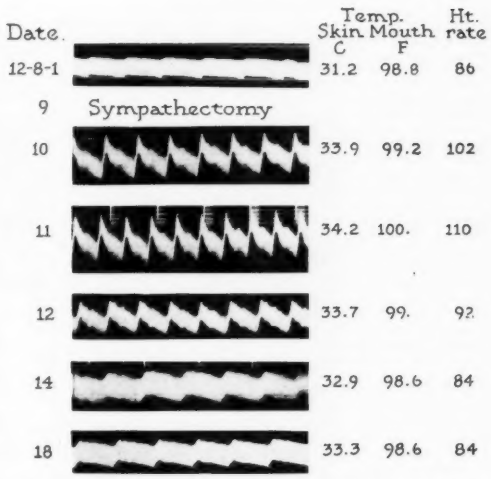


Fig. 1. B.C. The effects of removal of the stellate and second dorsal sympathetic ganglia on the finger volume changes and skin temperatures of the third finger. Note the return of the finger volume changes to the pre-operative level in 21 days in spite of the fact that the skin temperature remained elevated. (From Surg., Gynec. & Obst., 1932, Dec.)

Operations of the sympathetic nervous system. In 1932 Johnson, Scupham, and Gilbert published

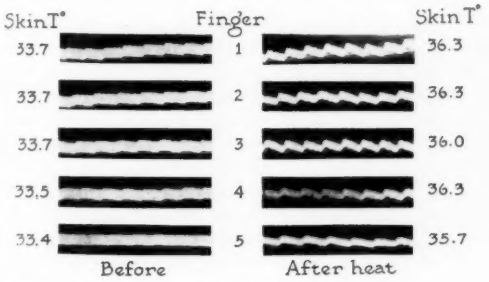
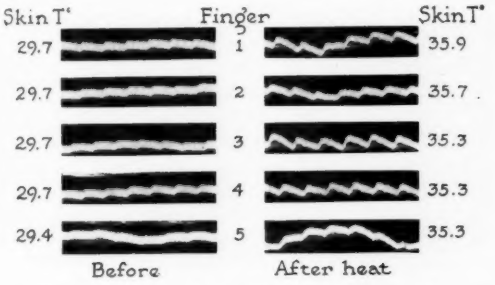


Fig. 2. B.C. The effects of local heat on the skin temperatures and finger volume changes of both hands 22 days following the removal of the right stellate and second dorsal sympathetic ganglia. Note that the skin temperatures



on the right side are higher than those of the left even though the finger volume changes in both hands are about the same. Also note that local heat produced about the same degree of vasodilatation on both sides.

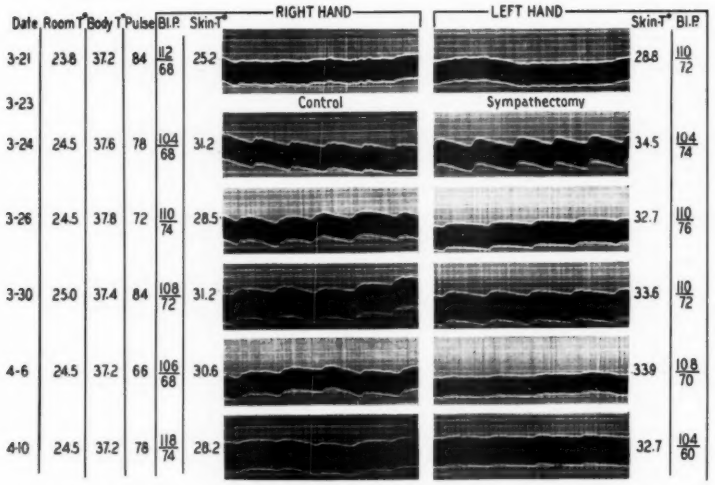


Fig. 3. T.A. The effects of removal of the stellate and second dorsal sympathetic ganglia on the body temperature, the skin temperature of the third finger of both hands, the pulse and blood pressures. The right side was used for a control. Note that the body temperature and pulse did not change appreciably; that the skin temperatures of the third finger of the left, which was also true of the other fingers, remained elevated above that of the right; and that the finger volume changes increased somewhat immediately following the operation, but in 18 days returned to their former levels. A similar operation was later done on the right side.

the results of removal of the stellate and second dorsal sympathetic ganglia in one patient and indicated that the peripheral circulation was improved only temporarily in this patient, thus confirming earlier experiments by others on animals. For the sake of completeness, a discussion of this first case is included with this report.

The types of operations performed were as follows: (1) unilateral removal of the stellate and second dorsal sympathetic ganglia; (2) bilateral removal of the stellate and second dorsal sympathetic ganglia, 2 cases; (3) bilateral removal of the stellate and third dorsal sympathetic ganglia, (4) bilateral preganglionic section of the sympathetic chain below the third dorsal ganglion, (5) removal of left stellate and second dorsal sympathetic ganglia and right preganglionic section of the sympathetic chain below the third dorsal ganglion.

The results of the studies of these patients are given as follows:

1. *Unilateral removal of the stellate and second sympathetic ganglia.* The results of the study of this patient have already been reported, but a brief review is included here to show follow-up studies and to correlate the findings with those of the 5 patients subsequently operated upon.

B. C., a white female, aged 22 years at the time of operation, was admitted to St. Luke's Hospital on August 28, 1929, with a diagnosis of long standing rheumatoid arthritis. The early manifestations of the disease started when she was 12 years of age, but subsided and were not severe until she was 18 years old. In spite of treatment, the disease progressed until all the joints except those of the spinal column were involved and deformed. Reports in the literature, at that time, indicated beneficial results from operations on the sympathetic nervous system. A unilateral removal of the stellate and second dorsal sympathetic ganglia was done by Drs. Carl Hedbloom and H. I. Meyer. Studies of the peripheral circulation were made before and at frequent intervals after the operation. No other therapeutic procedures were used for 2 months following the operation so that a proper evaluation of any beneficial result from the operation could be made. The patient showed no clinical improvement, but later had considerable improvement from corrective orthopedic procedures.

Figure 1 shows the marked increase of the finger volume changes immediately after the operation. The circulation had returned to the pre-operative level 21 days later, although the skin temperatures of the side operated upon remained above those of the control side. Figure 2 illustrates the effects of local heat to the hands before and 22 days after the operation. This record furnishes more proof that the peripheral circulation had returned to the pre-operative

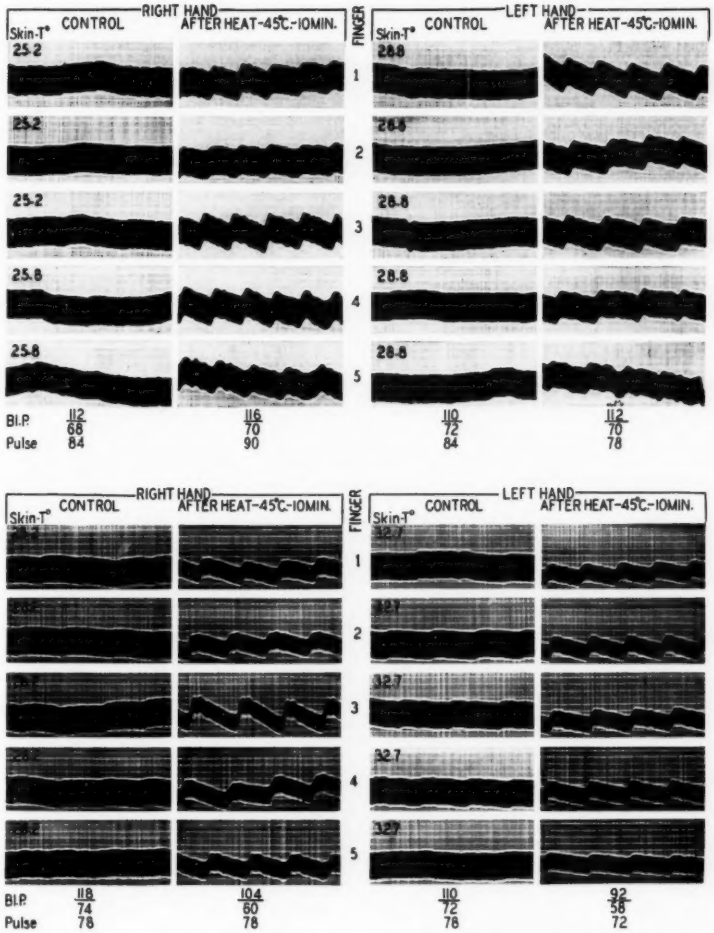


Fig. 4. T.A. The effects of local heat to the hands before, above, and 18 days after, below, operation on the blood pressures, the pulse rate, and the finger volume changes. Note that on both occasions the control finger volume changes were abnormally low and local heat caused about the same amount of increase both before and 18 days following operation. The control skin temperatures also were lower than normal. Note also the lack of correlation between the skin temperature and the finger volume changes of the left hand 18 days after operation.

level as local heat caused a vasodilatation similar to that preceding the operation.

Conclusion from this study is that the peripheral circulation returned to its pre-operative level within 21 days following the operation. Further conclusions will follow presentation of 5 additional cases.

CASE 1. Bilateral resection of the stellate and second dorsal sympathetic ganglia:

T. A., a white female, aged 33 years, was admitted to Passavant Hospital on March 23, 1936, on the service of Dr. Loyal Davis, for surgical relief of Raynaud's symptoms. Since November, 1932, the fingers of both hands had turned white, blue, and red, then normal. At first, only the second and third fingers of both hands had been involved to the second interphalangeal joints; later the second, third, fourth, and fifth fingers of both hands had become involved to the metacarpophalangeal joints. These attacks occurred mainly on exposure to cool air, but also to cold water, and during emotional spells as well as following cold

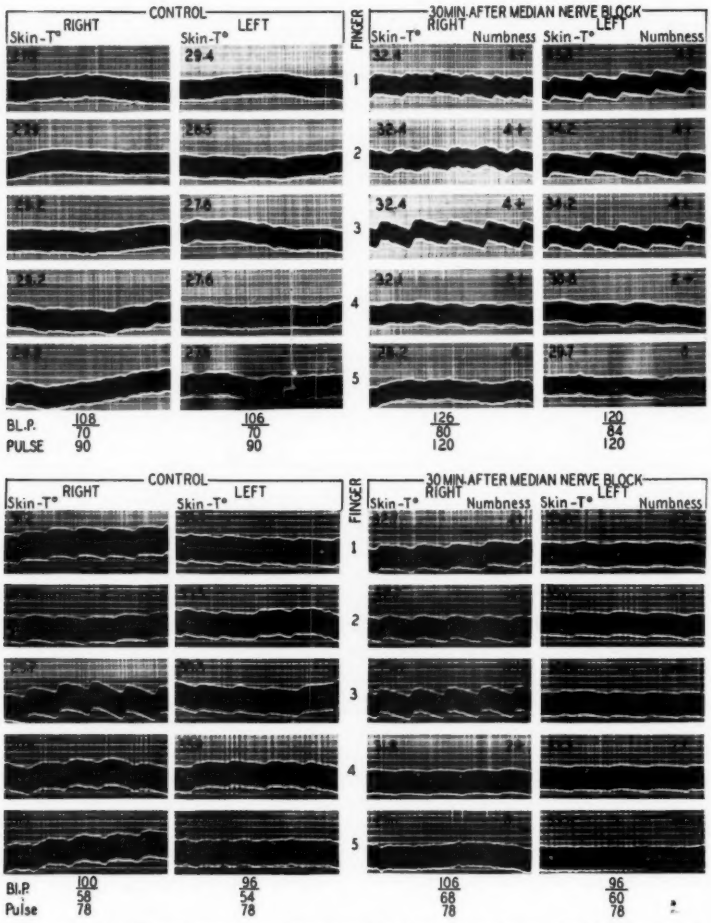


Fig. 5. T.A. The effects of median nerve block at the wrist on the blood pressure, pulse rate, and finger volume changes of both hands before, above, and, below, 17 days following removal of a left stellate and second dorsal sympathetic ganglia. Note that before the operation, the median nerve block produced an increase of the finger volume changes and increased skin temperature of the first three fingers and less so in the fourth, while in the fifth finger there was no change. Following operation, a satisfactory test could not be made because the patient became emotionally unstable. Even though a satisfactory nerve block was obtained as evidenced by the numbness, the finger volume changes did not become increased.

drinks, ice cream, or chilling of the body. The attacks were more frequent and severe in winter, but occurred in the summer too. There was some pain in the fingers during the white and blue stages and numbness during the red stage, which disappeared on recovery. The attacks were relieved by rubbing the hands together. No trophic disturbances were present except an ulcer on the second right finger which started in 1935 and still pained her, but no pus was present. She has several attacks per day which last from 5 to 15 minutes. The past history was negative. The physical examination was negative except for the stubby appearance of the fingers. All the peripheral vessels were easily palpable. The patient was noticeably unstable emotionally, and during vascular studies had hysterical attacks which sometimes lasted an hour. The laboratory findings were negative except for a −24 basal metabolic rate. Dr. Davis removed the left stellate and second dorsal sympathetic ganglia on March 23, 1936. The right arm was studied as a control. It is interesting to note that symptoms recurred 8 days following the opera-

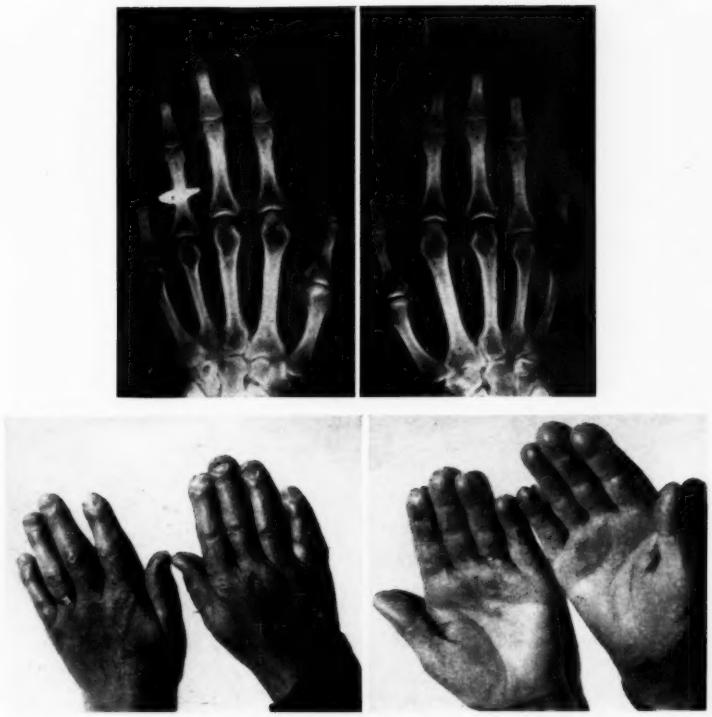


Fig. 6. M.B. Above, roentgenograms of the hands illustrating the sclerodactylia and bony changes in the terminal phalanges. Below, photographs of the hands showing scleroderma, changes in the fingernails, and loss of tissue on the ends of the fingers.

tion and at frequent intervals subsequently. A similar operation was done on the right side at a later date.

Measurements of the peripheral circulation were made before and daily after the operation until the finger volume changes had reached the pre-operative level: in 16 days as compared with 21 days in the previous case (Fig. 3). Here, too, the skin temperatures remained higher on the side operated upon. Figure 4 shows the vasodilating effects of heat before and 18 days following the left sympathectomy. The records are similar, indicating that the vessels had regained their pre-operative tone.

Figure 5 shows the effects which were produced by median nerve block on the finger volume changes before and 17 days following the left sympathectomy. Although the characteristic numbness occurred in the first three fingers of the left hand, there was no evidence of vasodilatation. This is offered as proof of the completeness of the operation.

CASE 2. Bilateral removal of stellate and second thoracic sympathectic ganglia.

M. B., white female, aged 47 years. I first saw her March 13, 1935 because of Raynaud's symptoms which had been present since the winter of 1930. All her fingers turned white to the metacarpophalangeal joints. They then turned blue, red, and back to normal. She did not remember having frozen the fingers. These attacks continued and became more severe in frequency and duration. In the winter they necessitated staying indoors virtually all the time; even then, she had two to three attacks daily. The attacks were caused most easily by cool air, less so by cool water. She remembered only one attack associated with an emotional upset. The attacks were relieved most easily by immersion of the hands in cold water, followed by warm water. The patient had numerous trophic disturbances and since 1931 had lost fingernails from the first, second, and third fingers of both hands. The past history was negative except for typhoid at 8 years, a rectal fistula at 25 years, and influenza at 30 years. Examination was essentially negative except for evidence of loss of tissue on the tips of the fingers, disturbance of growth of the fingernails, scleroderma, stiffness of the finger joints, and sclerodactylia (Fig. 6). Dr. Loyal Davis did a bilateral removal of the stellate and second thoracic sympathetic ganglia in January, 1934. For a time the patient thought she had improved, particularly as the warm weather set in. The

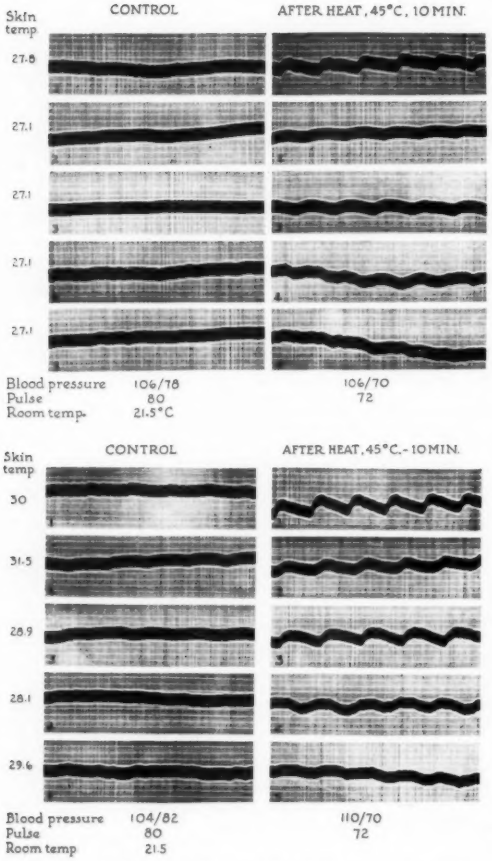


Fig. 7. M.B. The effects of local heat on the finger volume changes. Note the absence of pulsatile changes in the control records as well as no appreciable vasodilating effect of local heat particularly in the left hand. above. Bilateral removal of the stellate and second thoracic sympathetic ganglia had been done about 14 months before these records were made. Below, right hand record.

following winter the symptoms were as severe, or more so, than before the operation. The symptoms continued to progress in severity and duration and caused ulcers beyond the first interphalangeal joints. In June, 1936, treatment for an old syphilis was started. Since that time she has had complete relief of the Raynaud's symptoms although ulcers still occur on the fingers. The scleroderma has improved.

Studies of the peripheral circulation were made in the fall of 1935. Figure 7 shows the effects of local heat on the peripheral pulse volume changes. The small response before and after heat indicates marked organic changes in the peripheral vessels, especially in the left hand. Figure 8 shows the effects of median nerve block on the finger volume changes. This procedure produced an improvement of the circulation in fingers innervated by the median nerve. The operation should have destroyed the vasomotor fibers traveling in the median nerve. It is difficult to understand this result unless some vasomotor fibers still remained, or somatic motor fibers may be partly vasomotor in function. The patient does not perspire in the hands or arms. It does not seem likely, however, that regeneration of the vasomotor fibers would occur without regeneration of the sweat fibers.

This case is particularly instructive because it illustrates the inadequacy of our knowledge of the sympathetic nervous system as well as the pathogenesis of Raynaud's symptoms.

Case 3. Bilateral removal of the stellate and third sympathetic ganglia.

D. L., white female, aged 49 years, was admitted to Passavant Hospital April 18, 1938, as a patient of Dr. Loyal Davis, for the surgical relief of Raynaud's symptoms. She complained that for the past 3 years her fingers had turned successively white, blue, dark red, then back to normal. Similar symptoms did not occur in the toes. These attacks were brought on most easily by emotional spells, exposure of the hands to mild cold air, cool water, chilling of the body, and after she drank cold drinks and ate cold foods. There was a numbness but no pain during these symptoms. The attacks would occur most frequently in the winter, but some took place in the summer too. They were relieved by immersion of the hands in warm water. If this were not done, the attacks lasted until she overcame her emotional spell. The past history was negative except for attacks of migraine which began at the age of 16 years and continued until she was 45 years. The menopause occurred at the age of 45 years.

The physical examination was essentially negative. Roentgenograms of the chest and an electrocardiogram showed normal records. The results of the laboratory examinations are shown in Table II. The radials, ulnars, dorsalis pedis, and posterior tibial arteries were easily palpable.

The pre-operative studies on the peripheral circulations are illustrated in Figures 9 and 10. The vessels of the fingers were spastic and the plethysmographic records showed little or no pulsations. This was relieved by the application of local heat. The vessels were spastic at the time the effects of the median nerve block were being measured. Although a block was produced with the characteristic numbness of the first three fingers of both hands, relief of the spasm did not occur. This is difficult to explain as there is only one other patient in whom median nerve block failed to relieve a functional spasm of the vessels to the first three fingers.

On April 20, 1938, Dr. Davis resected the stellate and third dorsal sympathetic ganglia from which the patient made an uneventful recovery. Measurements of the peripheral circulation were repeated after operation. The effects of local heat were measured on June 21, 1938, by similar procedures. The results, as shown by Figure 9, indicated the vessels were more spastic than before the operation. The Raynaud's symptoms had recurred. The effects of median nerve block were measured on October 5, 1938, and at this time (Fig. 10) it was possible to obtain a

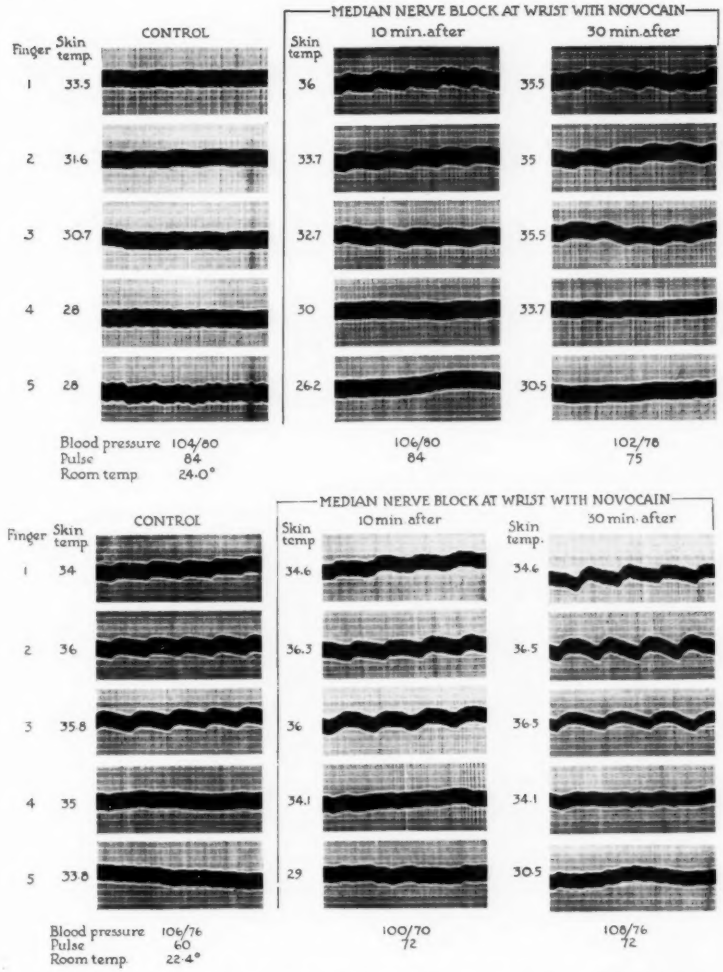


Fig. 8. M.B. The effects of median nerve block on the finger volume changes, skin temperature of the fingers, pulse rate, and blood pressure. Note the moderate vasodilating effect of this procedure in the first 3 fingers of both hands as well as an increased skin temperature in these fingers. The finger volume changes of the fourth and fifth fingers did not change. In the fourth and fifth fingers of the right hand, below, the skin temperatures decreased, which is the usual finding in normal individuals from this procedure. Above, left hand record.

release of the vasospasm, even though theoretically, this should not occur following extensive surgery on the sympathetic nervous system. Three winters have elapsed since the operation. The Raynaud's symptoms are as severe as before the operation.

CASE 4. Bilateral pre-ganglionic section of the sympathetic chain below the third dorsal ganglion.

Mr. Y, white male, aged 47 years, was first seen on May 25, 1937, for Raynaud's symptoms. In 1932 he noticed that all the fingers turned white to the metacarpal phalangeal joints, then passed through the various stages of blue, red, then normal. The symptoms had their onset in the toes also at the same time as in the fingers. They were brought on most easily by cool air, chilling of the body, or during emotional attacks, but were not affected by cold drinks. During the attacks he occasionally fainted. The Raynaud's symptoms lasted from a very short time to several hours, when nothing seemed to relieve them. The

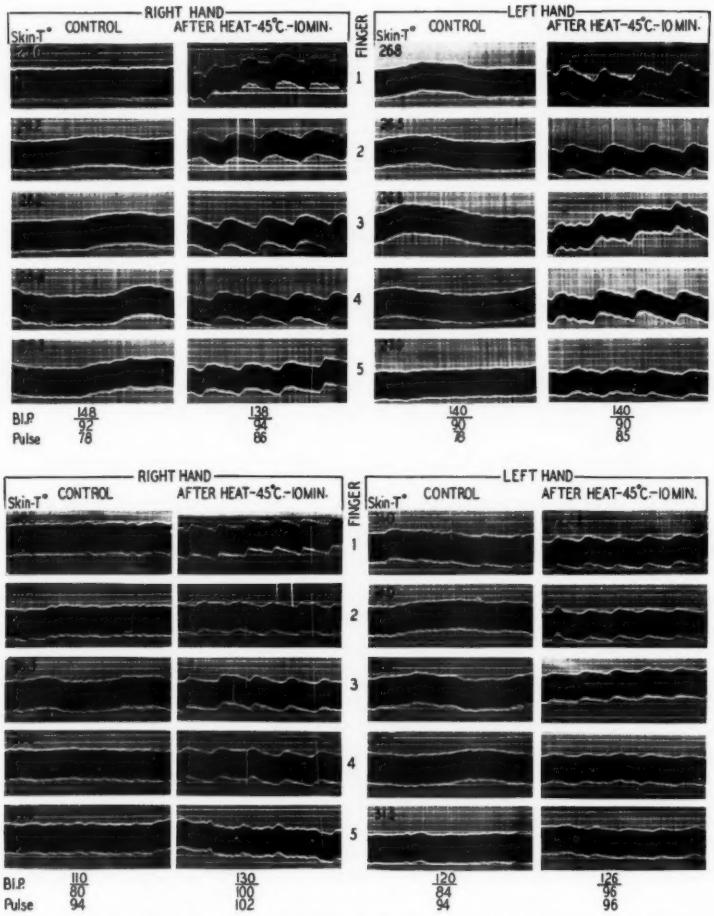


Fig. 9. D.L. The effects of local heat to the hands on the finger volume changes before and 63 days following the bilateral removal of the stellate and third dorsal sympathetic ganglia. Note the absence of pulse volume changes in the controls both before, above, and after, below, the sympathectomy in spite of the increased skin temperature following the operation; the local heat produced about the same amount of vasodilatation before and after the operation.

attacks usually were relieved by immersion of the hands in warm water, shaking of the hands, or exercise. The condition was worse in winter and comparatively absent during the summer.

In February, 1936, a bilateral lumbar sympathectomy was done at the Hines Hospital by Dr. Davis. This changed the character, but not the severity, of the symptoms. The toes no longer turned white, but the stinging sensation in the toes persisted. The most distressing symptoms which occurred since the operation were profuse night sweats of the legs followed by a sensation of extreme cold to the touch. The physical examination was essentially negative except with reference to the extremities. The radial, ulnar, posterior tibial, and dorsalis pedis arteries pulsated normally. Studies were made of the peripheral circulation (Figs. 11, 12, and 13). These results indicate there was no significant organic pathology in the peripheral vessels.

On June 11, 1937, Dr. Davis did a bilateral preganglionic section of the sympathetic chain below the third dorsal ganglia according to the method described by Smithwick. Detailed postoperative studies of the peripheral circulation were made (Fig. 11). These results show that peripheral circulation had returned to pre-operative level in about 12 days. It is interesting to note that the sweating function in the arms and hands had returned in about 6 days.

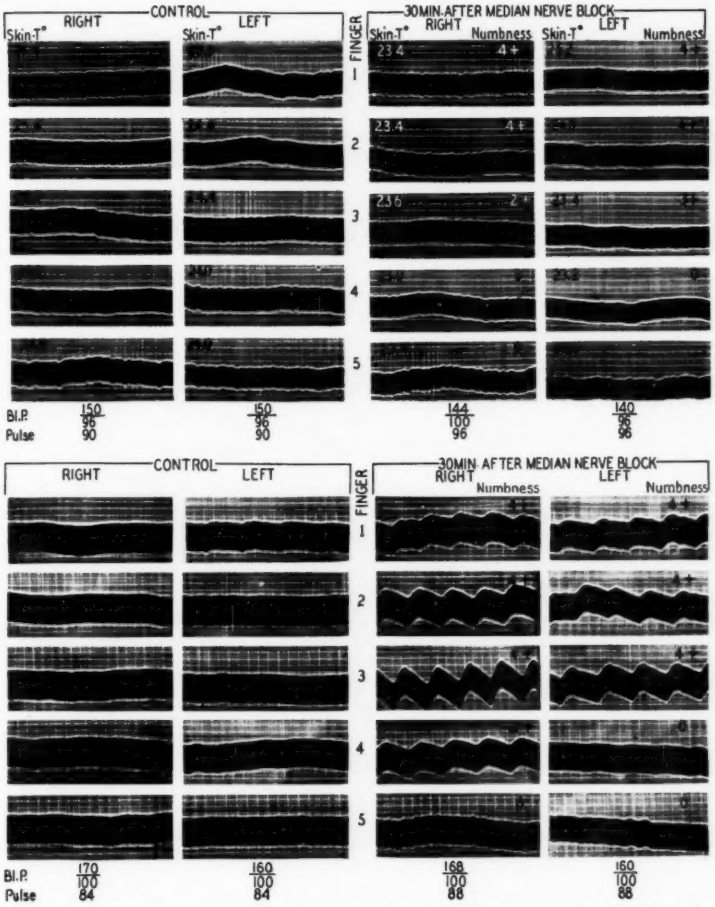


Fig. 10. D.L. The effects of median nerve block with novocain at the wrist on the finger volume changes before, above, and, below, 168 days following a bilateral removal of the stellate and third dorsal sympathetic ganglia. Following the injection of novocain during the experiment as illustrated in the upper record, the patient felt faint and a severe attack of Raynaud's symptoms occurred in spite of a good nerve block as illustrated by the characteristic numbness in the first three fingers. Note the absence of pulse volume changes in both the control and after median nerve block in the upper record; the low skin temperatures before and after nerve block which is not the normal response in the first three fingers. The patient had typical Raynaud's symptoms during nerve block in the first three fingers of each hand. In the lower record there is an absence of finger volume changes in the control records. Following median nerve block, vasodilatation occurred in the fingers innervated by the median nerve, in the apparent absence of sympathetic vasomotor nerves. The patient had a persistent absence of sweating in the upper extremities indicating the completeness of the operation. The median nerve block induced a Raynaud's attack in the fifth fingers, apparently from diversion of blood to the other fingers.

The effects of local heat were measured before and 12 days after operation, and of the median nerve block before and 14 days after operation (Figs. 12 and 13). The results indicate that the peripheral vessels were able to dilate following the operation just as before, indicating the circulation had returned to the pre-operative level. Beneficial effects of the operation were only transitory for the symptoms recurred within 1 month and continued to be as severe

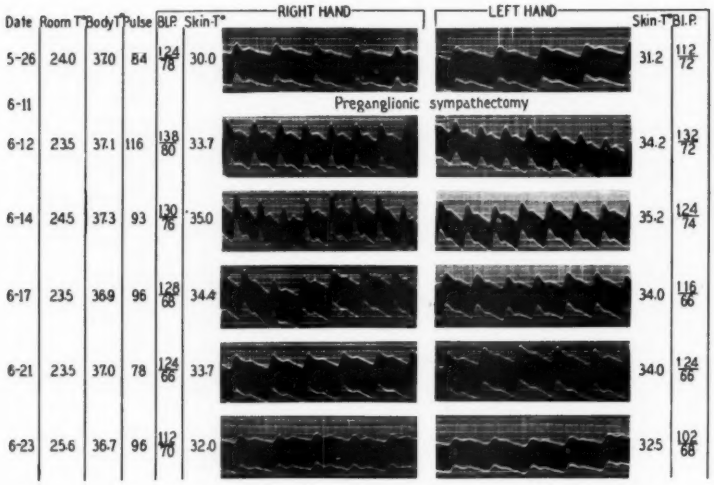


Fig. 11. Y. The effects of the preganglionic type of sympathetic operation in which the sympathetic chain was severed below the third thoracic on both sides. Note that there were no changes, vascular or otherwise, which persisted beyond the traumatic effects of the surgery.

or more so than before. He now has intractable headaches associated with the Raynaud's symptoms and often faints. Last winter, an attack of Raynaud's symptoms lasted about 2 hours and could not be relieved by the usual methods.

It is interesting to note that his 16 year old son now has occasional attacks of Raynaud's symptoms.

The results in this case indicate the inadequacy of surgical procedure for the relief of the patient's symptoms.

CASE 5. Removal of left stellate and second dorsal sympathetic ganglia and right preganglionic section of the sympathetic chain below the third dorsal ganglion.

H. H., white female, aged 36 years, was admitted to Passavant Hospital on the service of Dr. Loyal Davis for surgical relief of Raynaud's symptoms. Her complaints were that all of her fingers turned white, then blue, red, and then finally normal. She had frequent headaches, dizziness, and congestion, and soreness in the eyes. The attacks of Raynaud's symptoms began in her hands and feet at the same time about 8 years previously. She did not know whether the attacks were worse in the hands or feet, but her attention was drawn mostly to her hands. Here the attacks were brought on most easily by exposure to cool air, less so by emotional spells, and less so by immersion of the hands in cold water. They were relieved most easily by exposure to warm air and water, and would even end spontaneously. The attacks necessitated staying indoors during the cold weather but would occur frequently in summer too.

No pain accompanied the attacks, but during the white stage the fingers felt cool and numb. Recovery with warm air left no further subjective symptoms. On the other hand, when the hands were placed in warm water, produced a sensation of "pins and needles" in the fingers.

Physical examination was essentially negative except that the hands appeared swollen. The peripheral vessels were easily palpable and pulsating. The results of laboratory studies are reported in detail in Table II. The abnormal findings were: sedimentation rate, 14; basal metabolic rate, −18; and a mild secondary anemia.

Studies of the peripheral circulation by means of the digital plethysmograph showed that the effects of local heat and median nerve block before operation were a moderate organic change in the peripheral vessels.

On July 30, 1938, the stellate and second dorsal sympathetic ganglia were removed on the left side while on the right a preganglionic section was done according to the method of Smithwick.

Studies of the peripheral circulation were made daily following the operation until the circulation had reached its pre-operative level 8 days later (Fig. 14). The effects of local heat on the finger volume changes were measured 21 days after operation and were similar to the pre-operative records (Fig. 15). The effects of median nerve block also were measured 39 days after operation and, just as before the operation, the nerve block did not relieve the spasm in the fingers although the characteristic numbness occurred following the block. These results are similar to those of Case D. L.

ANALYSIS OF STUDY

The symptom complex now known as Raynaud's disease is very little understood in spite of the tremendous amount of study it has received since the original publications of Raynaud. The main reasons for this apparent lack of progress in our knowledge are: (1) opinion differs as to whether Raynaud's disease exists as a clinical entity; (2) the nature of the vascular changes are

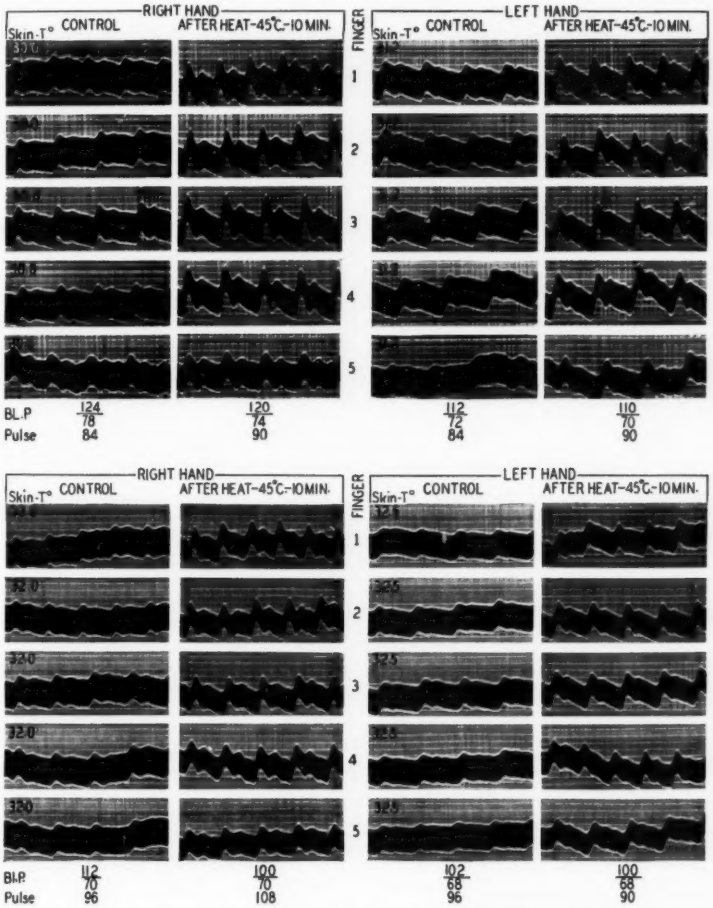


Fig. 12. Y. The records show the effects of local heat on the finger volume changes before, above, and, below, 12 days following the operation and one notes that about the same degree of vasodilatation is induced on both occasions.

not understood; and (3) opinion differs regarding treatment. This discussion is based on a study of the 22 patients reported in this article.

A. Does Raynaud's disease exist as a clinical entity? This answer is of fundamental importance, for it not only forms a common ground for the study of the symptom complex, but also would tend to rationalize understanding of the nature of the vascular changes, as well as the treatment of the symptom complex.

Hutchinson, more than 50 years ago, concluded that what is known as Raynaud's disease does not exist as a clinical entity and the peripheral manifestations observed are merely symptoms of some more fundamental disease. Hunt, in a more recent review of the subject, came to essentially the same conclusions and added that if Raynaud's disease exists at all, it must be very rare. He had no solution for a change in terminology. He believes that the term "Raynaud's disease" has such common usage it is doubtful it could be replaced by a more accurate descriptive term, such as Raynaud's syndrome.

The author arrives at the same conclusions from a study of the patients reported in this series, but is aware that persons examining these

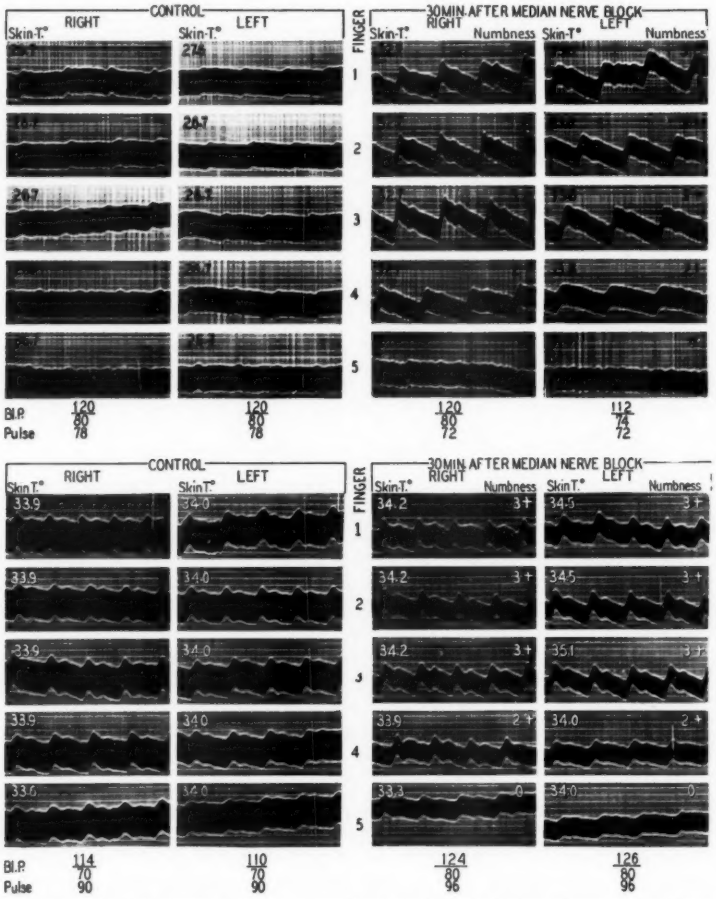


Fig. 13. Y. The effects of median nerve block at the wrist before, above, and 14 days after, below, operation mentioned in the legend under Figure 11. Note that it was possible to produce a vasodilatation in the fingers innervated by the median nerve both before and after the surgery.

reports may doubt the accuracy of the diagnosis in many of the patients, as has occurred with Raynaud's original series. Certain data in these studies, however, throw light on the nature of the vascular changes during Raynaud's attacks and further bear out the opinion that the changes observed in the extremities of patients with Raynaud's attacks are merely symptoms of some more fundamental disease.

B. The nature of the vascular changes in Raynaud's syndrome. The generally accepted view is that the blanching of the fingers or toes during a Raynaud's attack is caused by an *active* peripheral vascular constriction. The results of these studies indicate this may not be strictly so.

It is conceivable that the symptom complex in the fingers during a Raynaud's attack may be caused, in part, by a vasodilatation in the palmar arch and a passive collapse of the vessels in the fingers from an inadequate amount of the blood and blood pressure to keep them open. In other words, the blood may be shunted into the palmar arch without going through the fingers. The data in support of these ideas are as follows:

1. During a Raynaud's attack, it has been widely observed that radial pulse does not change.

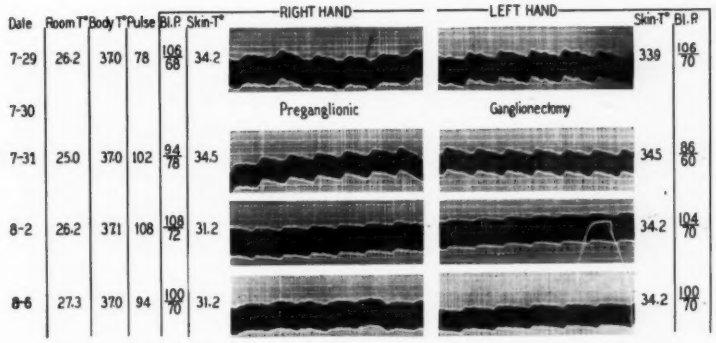


Fig. 14. H.H. The effects of a preganglionic type of operation on the right side and removal of the stellate and second dorsal sympathetic ganglia on the left side on the body temperature, skin temperature, blood pressure, pulse, and finger volume changes. Note that the finger volume changes returned to the pre-operative level within 8 days, and that the skin temperature on the right side went below the control level while on the left it remained above the control level.

2. Blood can be diverted from the fingers in a normal individual by the administration of amyl nitrite, as shown in 1932 (3). A vasodilator drug which produces a vasodilatation in one place may produce a *passive* vasoconstriction in another if it causes sufficient diversion of blood to one area with a further resulting fall in blood pressure. In this particular case the amyl nitrite causes a diversion of the blood to the splanchnic area and a fall in blood pressure with insufficient blood and blood pressure to keep the finger vessels open. A similar phenomenon may exist in Raynaud's syndrome as a result of diversion of blood through the palmar arch.

3. One of the effects of median nerve block at the wrist and increased skin temperature is a vasodilatation in the first three fingers, less in the fourth finger, and a decrease in the fifth finger with a fall in skin temperature. The decrease in the circulation in the fifth finger from this procedure is caused by a diversion of blood to allow more blood to pass into the first three fingers. In patients with Raynaud's syndrome the same changes occur. A typical Raynaud's attack frequently occurs in the fifth finger alone. The most apparent explanation for this is that blood diverted from the fifth finger produces a Raynaud's attack, and not an active vascular constriction.

4. In patients with Raynaud's syndrome during periods of freedom from attack, measurements of the circulation of the fingers show a circulation less than normal even in the absence of any organic vascular changes. Under such circumstances it would seem logical to conclude that it would not require as much diversion of blood to produce a Raynaud's attack as it would in a normal individual. The average amount of blood received by the five fingers under normal conditions is approximately 3.6 cubic centimeters of blood in one minute. In many patients with Raynaud's disease reported in this series, between attacks and under similar environmental conditions, the amount was far less, and measurements indicated that the amounts varied from less than 1 cubic centimeter per minute to the normal 3.6 cubic centimeters.

5. Patients with organic vascular changes who have Raynaud's syndrome suffer more distress from the attacks. It may be that even a lesser diversion of blood from the fingers can produce a Raynaud's attack.

6. If the lesser diversion of blood from the fingers can produce a Raynaud's attack, one cannot expect surgical removal of the vasoconstrictor fibers to the extremity to eliminate the attacks. This is shown by the poor results in 5 patients of this series.

7. Finally, there is so little direct evidence that the sympathetic nervous system is at fault in patients with Raynaud's syndrome, and considerable evidence that the humeral mechanism of peripheral vascular control may be impaired. Further study is indicated in this direction. The evidence of the importance of changes in the blood inducing Raynaud's attacks will be discussed in more detail under "The Treatment of Raynaud's Syndrome."

C. The association of other diseases with Raynaud's syndrome. Other conditions or diseases are common with Raynaud's syndrome. In these

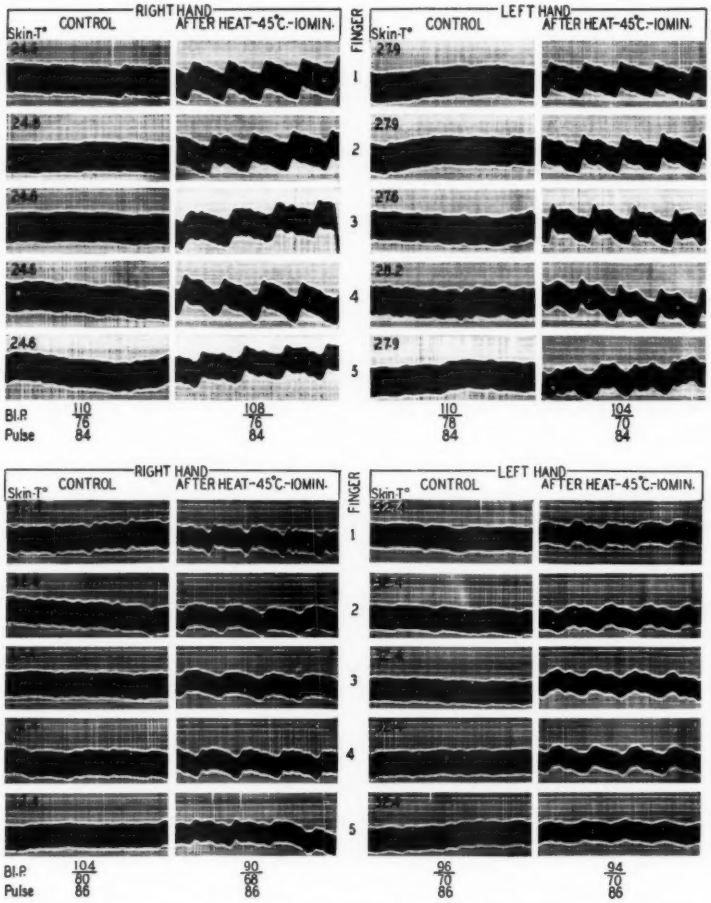


Fig. 15. H.H. The effects of local heat to the hands before, above, and 20 days following, below, operation on sympathetic ganglia. Note the very low amplitude of the finger volume changes in the control records both before and after surgery, and that finger volume changes were increased by the application of local heat in both cases.

series the following were found: (1) secondary anemia—mild, 13 cases; severe, 2 cases; (2) syphilis, 2 cases; (3) organic vascular disease—peripheral vascular, 12 cases; cardiovascular, 3 cases; (4) trophic disturbances—ulcers on fingers, 5 cases; stiff finger joints, 5 cases; loss of fingernails, 4 cases; skin, scleroderma, 5 cases; bones, sclerodactylia, 3 cases.

This common association with other diseases immediately presents two questions: (1) How much does secondary anemia or syphilis contribute to Raynaud's symptoms? (2) Do the Raynaud's symptoms lead to organic vascular changes and trophic disturbances or do they have a common etiology with these changes?

These questions can only partially be answered from observations of patients in this series. As to the first, the treatment of a mild or severe anemia resulted in improvement in all. The degree of improvement varied from slight to almost complete relief from attacks. Syphilis is occasionally associated with Raynaud's symptoms, and was present in 2 patients in this series. The effects of antiluetic treatment could not be observed in one of these patients because he did not stay under observation. In the other, who also

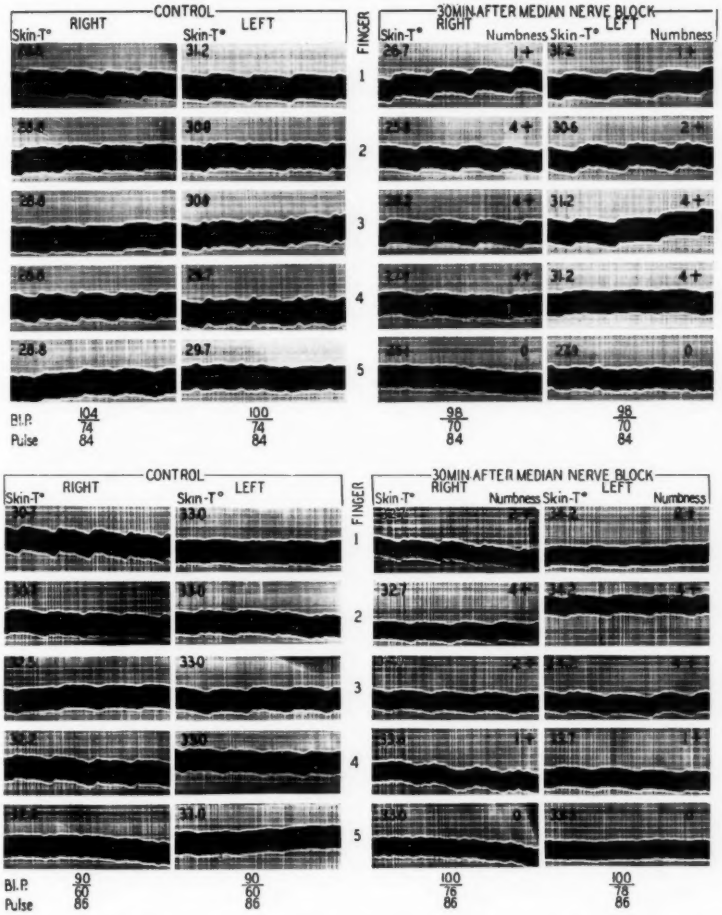


Fig. 16. H.H. The effects of median nerve block at the wrist before, above, and, below, 39 days following operation on the sympathetic ganglia. Note that the block did not produce the characteristic increase in finger volume changes in the fingers innervated by the median nerve, either before or after surgery, that the patient did experience the characteristic numbness in the fingers following the block, that the skin temperatures did not change appreciably, and showed no definite correlation with the finger volume changes and that injection of the median nerve induced a typical Raynaud's attack during the course of the experiment as illustrated by the upper record.

had scleroderma and sclerodactylia, complete relief from the Raynaud's symptoms and great improvement of the scleroderma followed antiluetic treatment. Here a common etiology for the Raynaud's syndrome and the associated diseases is suggested. Organic vascular disease, present in a number of patients, varies from mild organic peripheral changes to severe cardiovascular disease with decompensation. One must ask: (1) How much of the organic changes are secondary to the Raynaud's symptoms? (2) Are the Raynaud's symptoms secondary to the organic vascular changes? (3) Do the Raynaud's symptoms and the organic vascular changes have a common etiology? The results of this study indicate they have a common etiology.

D. The treatment of Raynaud's syndrome. The treatment of Raynaud's syndrome varies with

circumstances as determined from each individual case but may follow certain broad principles, as follows:

1. No treatment necessary. In a group of patients (5 in this series), no definite etiology can be found, the symptoms are mild, and the Raynaud's syndrome shows no evidence of progression even after many years. Patient S. T. of this series illustrates this very well. She has been under observation for Raynaud's symptoms for 10 years. There has been no progress, the symptoms are very mild, and she has learned to avoid the attacks. In the meantime, she has developed a cancer of the breast which is more distressing than the Raynaud's disease.

2. The treatment of associated diseases. It is very important to treat associated conditions or diseases, particularly secondary anemia and syphilis. The secondary anemia obviously involves the treatment of the cause of the anemia if it can be found.

3. Local treatment. This involves instructions to the patient to avoid the thing that brings on the attacks. Paraffin baths give considerable relief to some patients.

4. Surgery of the sympathetic nervous system. In 5 patients in the series, various types of surgery to the sympathetic nervous system were performed. No improvement was noted, as judged over a period of years. Some reasons for this are in the next heading.

E. Notes on the early and late vascular effects of surgery to the sympathetic nervous system. These effects vary with the type of operation done as follows:

1. The effects of resection of the stellate and second or third dorsal sympathetic ganglia. Immediately following this type of operation there are present, (a) an increased skin temperature of the upper extremity, (b) cessation of sweating to the upper extremity, (c) an increased circulation in the fingers, and (d) a Horner's syndrome. Heat regulation and circulation are altered.

In 12 to 35 days, the circulation returns to the pre-operative level but the skin temperatures remain elevated and the absence of sweating persists. This occurs in the apparent absence of the sympathetic vasoconstrictor tone. The function of the sympathetic vasoconstrictor fibers is probably taken over by the other factors which serve to maintain the peripheral vascular tone, such as the local vascular nerves, the independent tone of the blood vessels, and the humeral mechanism. Too, somatic nerves may have a vasomotor function, for in 2 cases following the type of operation just mentioned, it was possible to produce a vasodilatation in the course of the median nerve by nerve block at the wrist.

2. Following the so called "preganglionic sympathectomy" to the upper extremity as done by White (1), the circulatory effects as well as any effects on heat regulation were transitory: it is doubtful that they lasted longer than the traumatic effects of the operation. Vasodilatation in the fingers could be produced following recovery from the surgery by local heat or median nerve block indicating the presence of nerves with vasomotor function.

It is difficult to reconcile many of the views expressed with some of those of the literature, especially those concerning treatment. One can say definitely that in this series of patients, medical management offered far more to the patient in the way of objective and subjective relief than surgery.

The importance cannot be overlooked of the recognition of patients with Raynaud's symptoms as part of some other disease as compared with the recognition of Raynaud's disease (*which may not even exist as a clinical entity*).

If Raynaud's disease exists as a clinical entity, it must be very rare; it is doubtful if any of the patients reported in this series had the disease. If this is true, the author never has seen a patient with unquestioned Raynaud's disease.

On the other hand, 22 patients are reported with Raynaud's symptoms as part of some more fundamental disease. Medical management gave a great deal of relief to a number of these patients. It would seem logical to conclude that it would be better to direct our attention to the recognition and treatment of Raynaud's symptoms as part of some other disease than to Raynaud's disease per se, which must be extremely rare if it exists at all.

SUMMARY AND CONCLUSIONS

The results of a study of 22 patients with Raynaud's syndrome are presented with the following opinions.

1. Observations on this series of patients confirm Hutchinson's statement made more than 50 years ago that what is known as Raynaud's disease is not a clinical entity, and that the peripheral manifestations observed are merely symptoms of some more fundamental disease.

2. The vascular changes during a Raynaud's attack are not necessarily due to an active vascular constriction, but may be the results of a vasodilatation in the palmar arch with a diversion of blood from the fingers and a passive collapse of the vessels.

3. In this series of patients, surgery of the sympathetic nervous system was a therapeutic failure but medical management gave considerable relief in a number of patients.

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MUCINOUS CARCINOMA OF THE BREAST

OTTO SAPHIR, M.D., Chicago, Illinois

IT is often amazing to observe, within an outspoken malignant epithelial tumor, glandular or cystic structures filled with a basophilic homogeneous material in which perhaps only a few groups of carcinoma cells are still recognizable. From adjacent structures having adenocarcinomatous portions, one gains the impression that perhaps this evidently secreted material has led to an atrophy and the eventual destruction of the tumor cells. In other words, the mucin which originally had been secreted by the tumor cells had subsequently caused their disappearance. Apparently, because of the intriguing assumption of a seeming self-destruction of cancer cells, this type of carcinoma was early recognized as a separate variety of carcinoma, especially in the breast. As early as 1852 investigators classified this cancer of the breast as an especially benign form principally because of the conception of the destruction of the tumor cells by their own secretions.

Though this carcinoma early was recognized as a special type, until recently relatively few studies have been undertaken of mucinous carcinoma of the breast. The more recent interest in this entity may perhaps be traced to the studies of Cheatle and Cutler who showed that "mucinous degeneration" in breast carcinomas is more common than is generally supposed and emphasized that the presence of "gelatinous degeneration" in these tumors does not necessarily imply a low degree of malignancy, as was generally supposed.

The nomenclature of these tumors is confusing. The terms colloid, gelatinous, mucoid, mucinous, and myxomatous are used indiscriminately. It seems that since mucin is the product of epithelial cells the only correct term to designate these tumors is "mucinous," because these tumors are epithelial in nature and evidence of secretion is often noticeable in the individual tumor cells. Karsner emphasized the correctness of the term mucinous carcinoma. Furthermore, the staining reaction is more characteristic of mucin. According to Karsner, the term "colloid" is used because of the brown color and gelatinous consistency. "Colloid" should be reserved for tumors of the thyroid gland and hypophysis which secrete colloid. "Mucoid," meaning resembling mucin, does not occur in epithelial tumors but is seen particularly commonly in connective tissue tumors. "Gelatinous" is purely a descriptive term referring to the similarity of the material to gelatin, but does not denote a specific substance. Yet Ewing, contrary to this, stated that true mucin is found chiefly in connective tissue tumors, pseudomucin in epithelial growth. From the foregoing, it is clear that the more correct term for these tumors is "mucinous" carcinoma, which nomenclature will be strictly adhered to.

An opportunity presented itself to study several instances of mucinous carcinoma. Surgical specimens and autopsy material from patients who had died from this carcinoma were available. Particularly because of the latter and because it was soon realized that what was thought to constitute one group of tumors in reality consisted of several types of carcinomas, it was thought of interest to report the results of this study.

A complete review of this subject does not seem necessary. Geschickter recently reviewed in detail the available data. It may be of interest, however, to mention that as early as 1852 and 1853 Lebert, Larrey, and Robinson had studied mucinous carcinomas and stressed the slow growth of these cancers. Later, curiously enough, the interest in these tumors culminated in the purely theoretical question as to whether the mucinous, or as it was called—colloid material, took its origin from the epithelial cells or from the connective tissue framework. Even among the earlier investigators there were a few who doubted the entirely benign course of these breast carcinomas. Gaabe, 1908, remarked that occasionally the mucinous carcinoma may lose its mucinous characteristics, its cells may take on a high degree of anaplasia and the tumor may revert to a carcinoma of the usual type. But Shepherd, 1938, still emphasized that gelatinous carcinoma of the breast is of low malignancy and is easily cured by radical excision; but if recurrence takes place, the prognosis is bad because of the insistence of the growth.

Cheatle and Cutler, 1931, reported 10 instances of mucinous carcinoma of the breast. They remarked upon the prevailing opinion that this is the least malignant form of a mammary carcinoma, that metastases occur late, and that the

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From the Department of Pathology of the Nelson Morris Institute, Michael Reese Hospital.

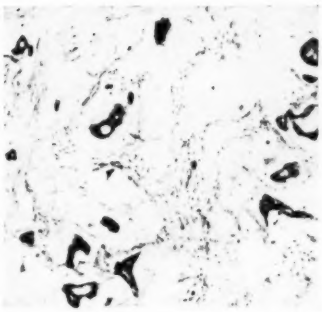

Fig. 1. True mucinous carcinoma. Note the islands of tumor cells. (There are no other types of tumorous structures). Iron hematoxylin-eosin preparation. ×37.

prognosis is more favorable. They specifically mentioned that with few exceptions the conception that this form of cancer may be highly malignant is not encountered in the literature. Five of their 10 tumors were among the most malignant, they stated, that can be encountered in the breast. Morphologically they were highly anaplastic and clinically their high degree of malignancy was demonstrated by prompt recurrence, widespread metastases, and rapid course. Lee, Hauser, and Pack, 1934, stressed the rarity of mucinous carcinoma of the breast. These investigators classified this carcinoma into (a) primary mucinous carcinoma in which the mucinous features predominate, (b) ordinary carcinoma with secondary mucinous degeneration. In these latter instances the mucinous degeneration may be recognized histologically only, whereas other portions may be highly malignant. The latter group again is subdivided into "myxoid carcinoma" in which the mucinous changes arise by metaplasia in the connective tissue whereby the latter becomes "myxomatous," and into "mucoid carcinoma,"

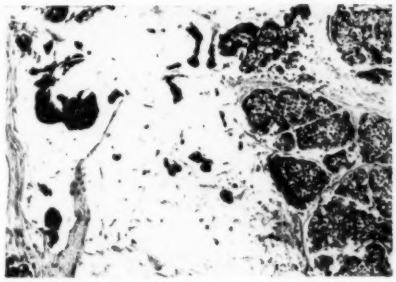

Fig. 3. Mucinous carcinomatous features in duct carcinoma. Note the duct carcinoma in the right part of the picture. Iron hematoxylin preparation. ×51.

Fig. 2. True mucinous carcinoma. Note the islands of tumor cells not exhibiting evidence of anaplasia, or mitotic figures. Iron hematoxylin preparation. ×155.

a variety in which the mucinous material originates directly from the carcinoma cells. It must be mentioned that this classification is made on presumptive evidence, since the authors did not offer evidence for the dual origin of the mucinous material. However, they refer to the observation of Ewing who described compact alveoli lying in broad areas of a mucous stroma with no evidence of mucous degeneration of the epithelium, as supporting the connective tissue origin of the mucinous changes. These authors also mentioned a mucinous type of tumor which has the structure of a papillary carcinoma.

Geschickter, 1938, classified these mammary cancers into two groups. In one, the tumors con-

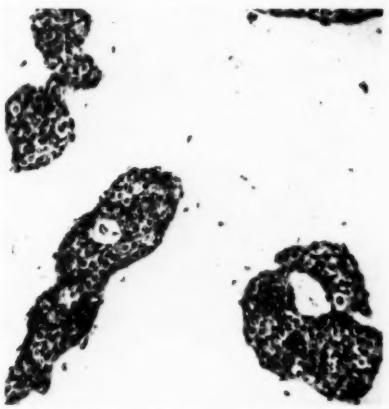

Fig. 4. Mucinous carcinomatous features in duct carcinoma. Other parts of this tumor show typical duct carcinoma. Note the islands of tumor cells and the absence of signet ring cells. Iron hematoxylin preparation. ×135.

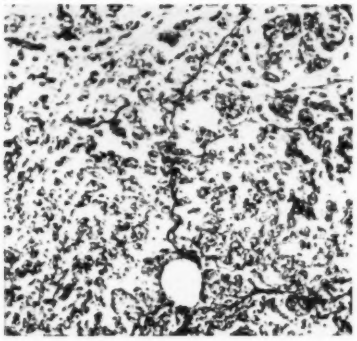

Fig. 5. Signet ring cell mucinous carcinoma. Note the abundance of typical signet ring tumor cells. Iron hematoxylin preparation. ×42.

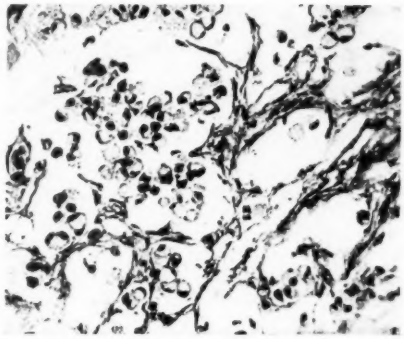

Fig. 6. Signet ring cell mucinous carcinoma. Note the signet ring cells within alveolar structures. Iron hematoxylin preparation. ×145.

tain a shiny, translucent gel throughout their substance and in the second group the gelatinous change is found in one or more portions, and solid, dense tissue in the remainder of the growth. It seems that Geschickter's classification is almost identical with that of Cheatle and Cutler, and also with that of Lee, Hauser, and Pack. Among those cancers in which the mucinous changes predominate, Geschickter, however, further mentioned a type which contains epithelium of the basal cell variety. Judging from the relatively benign character of the epithelium and from the large amount of mucinous substance, he believed that the prognosis is unusually good.

Gillespie and Schmeisser, 1939, also stressed the rarity of these tumors. They described 3 instances of mucinous carcinoma of the breast in which the mucinous changes were part of a medullary and of a duct carcinoma, respectively. They stressed the presence of mucinous material in adenocarcinomas of the breast, in intracystic papillary carcinoma, duct, and scirrhous carcinomas.

Ewing, 1940, stated that, as a rule, when mucous degeneration overtakes a tumor, while a rapid increase in size may follow, the tumor has reached the acme of its cellular activity and its malignancy is reduced. He stressed that mucoid carcinoma is a relatively benign form of cancer.

It may be mentioned in this connection that there have also been observed in our laboratory a number of carcinomas of the breast in which the connective tissue stroma was spread by an edema-like material, sometimes resembling mu-

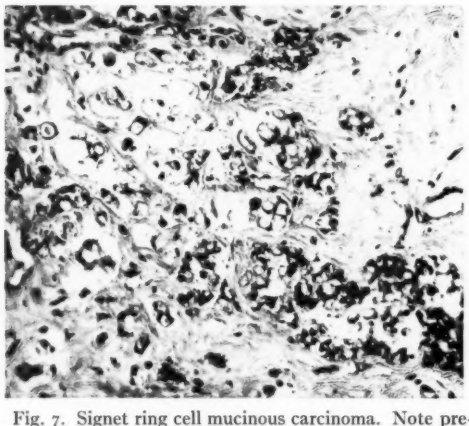

Fig. 7. Signet ring cell mucinous carcinoma. Note predominance of signet ring cells and also anaplastic tumor cells of duct carcinoma. Iron hematoxylin preparation. ×125.

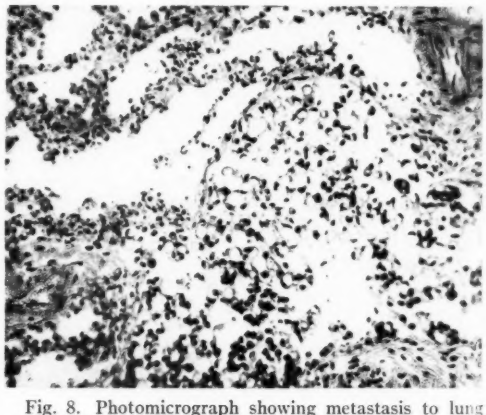

Fig. 8. Photomicrograph showing metastasis to lung of primary signet ring cell mucinous carcinoma. Iron hematoxylin preparation. ×102.

cin. These changes obviously involving the connective tissue stroma, not related to the carcinoma, do not form part of this study. These are merely mentioned here because of Ewing's statement that there are evidently two types of gelatinous carcinoma, one in which the mucinous changes have involved and partly originated in the fat tissue and stroma; and one in which the alveoli are filled with mucus.

This study is based on the postmortem examination of 2 patients who had died from widespread mucinous carcinoma of the breast, and on the examination of 7 breasts which had been removed for cancer which on histological examination also proved to be mucinous in character. In some instances sections of the whole breast or large portions of the breast were cut according to Cheatle's method. In other instances serial sections of the tumors and surrounding structures were made. The sections were stained with Delafield's hematoxylin and eosin or with Weigert's iron hematoxylin. Elastic stains (orcein) and the van Gieson stain were employed when deemed necessary. Also the mucicarmine stain for the presence of mucin was used.

It is not intended to give detailed clinical histories, and only essentials which seem important will be mentioned in connection with the pathological lesions encountered.

After all tumors had been examined, it seemed clear that the term "mucinous carcinoma" was rather broad and that undoubtedly various types of so called mucinous carcinoma existed. These tumors have been grouped and will be discussed accordingly.

True mucinous carcinoma. Of this type only one instance was observed.[1] Here large mucinous areas which apparently formed the bulk of the tumor were encountered. The outstanding gross changes were large, circumscribed, pale yellow areas which were of semifluctuant consistency and which were separated from one another by thin strands of fibrous tissue. Histologically most of the fields consisted of a pale bluish staining material often encased by a thin membrane, apparently the wall of a cyst. Hardly any cellular elements were seen and only occasionally epithelial cells with vesicular nuclei and basophilic cytoplasm were encountered, singly or clustered in small groups without any particular arrangement. As Lee, Hauser, and Pack expressed it, the cells were often "isolated in a sea of mucus." These cells showed no evidence of anaplasia and mitotic figures were rarely encountered. The lymph nodes were not involved. The patient was about 50 years of age. A radical breast resection was performed and the patient is in perfect health 7 years after the operation.

This tumor corresponds in every detail to the original description of mucinous carcinoma, and there seems to be no need of a more detailed description. This is the type which led to the conception of the benignity of these tumors. It very likely is an adenocarcinoma arising from the acini of the breast. The outstanding histological findings are the presence of the mucinous material with very few cellular elements and the absence of other malignant epithelial structures.

Mucinous carcinomatous features in duct carcinoma. This is perhaps the most common type of so called mucinous carcinoma and most of the reported tumors fall into this group. At least 7 of the 10 tumors reported by Cheatle and Cutler come under this classification. Of the 7 tumors removed surgically in this series, 5 must be designated as duct carcinoma with mucinous features.

Grossly these tumors may or may not be characteristic of mucinous carcinomas, though 4 of these 5 showed large, yellowish, semifluctuant regions similar to those seen in true mucinous carcinomas. But often, adjacent to these regions or sometimes in the middle of obviously mucinous areas, were firmer, grayish-pink, seemingly well circumscribed portions of tumor revealing bright yellow streaks. The extent of these two portions of which the tumor consisted varied considerably. The histological sections showed a mixture of typical duct carcinomatous structures and mucinous carcinoma. Large tumor cells with varying amounts of cytoplasm often filled small or larger ducts. Atypical mitotic figures were common and anaplasia was marked. Often groups of these cells were observed, more or less isolated and infiltrating the surrounding breast structures. In addition many cysts and dilated ducts were encountered, filled with a lightly stained basophilic material in which were groups of cells or isolated cells. These cells showed characteristics similar to those just described. Often, however, the nuclei were absent and mitotic figures were rarely encountered. Often within the cyst and within the mucinous material there were outlines of, or even well preserved, minute vessels and capillaries, though the tumor cells which must have been there before could not be made out. Sometimes the walls of these minute vessels were broken and many red blood corpuscles were seen within the cysts. It is of interest that in one of these tumors an intracystic papilloma and in another an intracystic papillary carcinoma were also present. It should be stressed here that the latter is met with not

[1] I am indebted to Dr. Paul Klemperer for this tumor.

rarely in outspoken duct carcinomas. The former probably is a coincidental finding and might not have been discovered had not the entire breast been examined.

As mentioned previously, "mucinous features" in duct carcinomas constitute the most common form of so called mucinous carcinoma. In these tumors the presence of mucin is apparently incidental and the tumor follows, as a rule, the course of a duct carcinoma. These tumors apparently belong to those mucinous carcinomas concerning which Ewing remarked that they may prove highly malignant. This he explained by the distention of tissue spaces by the mucus which distention supposedly facilitates the dissemination of the surviving cells.

Signet ring cell mucinous carcinoma. This type of carcinoma consists predominantly of secreting tumor cells. So much secretion is retained within the cells that they assume signet ring shapes. Three such tumors were encountered. One of these was a surgical specimen and the 2 others were found at postmortem examination. The surgically removed tumor was found beneath the nipple and consisted of a rather firm, ill defined mass measuring 4 centimeters in greatest dimension. The nipple was not fixed. On section the tumor was grayish-white but showed a few yellowish, glistening, and bulging areas. In the remainder of the breast foci of fibrosis and cysts were recognized. With the exception of these glistening areas there was nothing noted from which the mucinous character of the tumor might have been inferred. Histologically the tumor consisted mainly of well circumscribed foci of epithelial cells which showed either a lightly stained basophilic cytoplasm with nuclei situated at the base of the cells which often assumed the typical signet ring forms. Often the cytoplasm in the sections seemed clear, only the cell membranes and the crescent shaped nuclei being recognizable. In other fields small or larger cystic structures could be noted filled with a basophilic material and relatively few epithelial cells. However, instead of clumps of epithelial cells with clear cut, round nuclei and basophilic cytoplasm as seen in the true mucinous carcinomas, the cells suspended in the cystic structures here were signet shaped and had clear cytoplasm. These cells were also often seen isolated from ducts or acini, invading the stroma. Serial sections of the breast, however, also showed ducts which were crowded with tumor cells which either were typical of duct carcinoma cells with many anaplastic cells and numerous atypical mitotic figures or showed transition to signet ring cells as described. Some fields showed duct carcinomatous structures and adjoining these, accumulations of signet ring cells. Metastases to the axillary lymph nodes consisted only of the signet shaped tumor cells. The patient, a 55 year old white female, had noted the tumor only a short time before consulting the physician. A radical mastectomy was performed, not followed by radiation treatment and the patient, after 4 years, is apparently well.

A similar tumor was found in the 2 patients who came to autopsy. In the first instance, a 35 year old white female, a radical breast amputation had been performed 4 months before death. The autopsy revealed a local recurrence and metastases to the sternum, mediastinal lymph nodes, peritoneum, inguinal lymph nodes, liver, and both ovaries. As a matter of fact, both ovaries were so markedly enlarged—measuring about 12 centimeters in greatest dimension—that at first they were thought to be the seat of primary solid tumors. The tumors histologically consisted principally of slightly basophilic cells with flattened, crescent shaped nuclei. When the previously removed breast tumor was examined, sometime later, it proved to be histologically a duct carcinoma with transitions to the mucin secreting, signet shaped cells just described. In the second autopsy, the tumor was found in the left breast of a 49 year old colored female. It measured 4 by 5 by 5 centimeters in greatest dimensions, was of a rather firm consistency but was not noticed by the patient until shortly before she entered the hospital, where she died before treatment could be instituted. The autopsy revealed metastases in the axillary lymph nodes, pleura, lungs, pericardium, peritoneum, intestinal wall, retroperitoneal lymph nodes, suprarenal glands, ovaries, and spinal column. Histologically the breast tumor consisted mainly of signet ring cells either arranged in groups or singly, invading the surrounding stroma. However, serial sections also revealed outspoken duct carcinomatous structures. The metastases, however, consisted only of the signet ring cells.

Intracystic papilloma with mucinous features. Only one such tumor was observed. This was found in a 47 year old woman who had a small tumor in the left breast which suddenly became enlarged, at which time a hemorrhagic discharge from the nipple was noted. Grossly the tumor consisted of a cyst measuring about 4 centimeters in greatest dimension, which was filled with a hemorrhagic and mucinous material in which small, yellowish pieces of soft, granular tissue were found loosely intermingled. The inner wall of the cyst presented a rather soft and friable,

velvety, broadly attached tumor which consisted of a large number of well circumscribed, small or minute excrescences. These were covered and separated from one another by mucinous material. Histologically the tumor consisted of round, oval and, more often, spindle shaped epithelial cells resembling transitional cells of the urinary tract, and an insignificant, thin, connective tissue stalk. These cells were covered by a mucinous material and much of this was also present between groups of these cells. The wall of the cyst was well preserved. Because of the spindle shaped cells the tumor could be classified as a transitional type of intracystic papilloma (Saphir and Parker). Geschickter apparently drew attention to this type of tumor, to which he referred as gelatinous carcinoma containing epithelium of the basal cell type. He stated that judging from the relatively benign character of the epithelium and from the large amount of mucoid substance, the prognosis in these growths should be unusually good.

EVALUATION

It has been shown that the tumors classed as mucinous carcinoma of the breast are not one entity but apparently consist of various forms of tumors of the breast, four of which have been described. The true mucinous carcinoma, originally described as colloid or gelatiniform carcinoma is said to be of low grade malignancy. Only if sections through the whole breast or serial sections show no other types of malignant structures, may such a tumor be designated as true mucinous carcinoma. This form, however, seems the rarest. Not a single such instance was observed in this laboratory among over 700 cancers of the breast, the tumor described here having been received from another laboratory. Because of the insufficient material little can be said as to the origin of this type of cancer. It is probable that this tumor arises from the acini. This is apparent because of the histological finding of many small acini and the absence of duct structures which are so common in other forms of mucinous carcinoma of the breast. It is interesting to note that Geschickter described three tumors which microscopically are indistinguishable from basal cell cancer of the adenocystic type, such as is found in the parotid gland. A portion of the growth actually may resemble benign mixed tumors of the parotid gland. He believed that typical mucoid cancer of the mammary gland may originate as a form of adenocystic basal cell cancer. It seems quite possible that these tumors may be very early forms of true mucinous carcinomas of the breast. Perhaps the adenocystic structures described by Geschickter may constitute acini of the breast filled with mucin. The similarity of these early tumors to the adenocystic basal cell carcinoma is interesting because of the comparative benignity of these tumors and of the true mucinous carcinomas of the breast.

As mentioned before, the duct carcinoma of the breast with mucinous features is undoubtedly the most frequently encountered type of so called mucinous carcinoma. It seems that the mucinous changes are purely secondary, the underlying tumor being a duct carcinoma. In contradistinction to the third form, this variety shows the secreted mucin outside the tumor cells. The tumor cells are apparently soon destroyed and signet cells are not found. It is obvious that the degree of malignancy does not depend upon the presence or the amount of mucin but upon the unchanged duct carcinomatous structures.

Intracystic papilloma or intracystic papillary carcinoma are often found in these tumors, not only in this series but often in the tumors described in the literature. Though this finding offers some interesting speculation in regard to a possible relation of duct carcinoma and mucinous changes, to intracystic papilloma, this and other studies have not disclosed any relationship. It seems most likely that the simultaneous occurrence of these lesions is purely coincidental.

The signet ring cell variety is perhaps the most interesting and the two autopsy findings recall Cheatle and Cutler's statement that some of the mucinous carcinomas are among the most malignant tumors encountered in the breast. The widespread metastases in both autopsied cases, the rapid recurrence in the first, and the fact that when the second patient was seen, operation was too late because of the widespread metastases, indicates the high malignancy of these tumors. In both patients the ovaries were involved and studded with signet shaped tumor cells. It must be emphasized, of course, that in neither of the patients was a primary malignant tumor encountered in the gastro-intestinal tract, though metastatic tumors were found in the wall of the small intestine in the second patient. This suggests, perhaps, a peculiar affinity of these signet shaped tumor cells for the ovaries as seen in carcinoma of the stomach with signet ring cells—metastases to the ovaries (Krukenberg's tumor). On the other hand, however, it is interesting to note that one patient whose breast was radically removed for eradication of such a tumor is apparently well, four years postoperatively.

This variety of mucinous carcinoma is also found in combinations with duct carcinoma.

However, whereas in the signet cell variety the individual secreting tumor cells remain intact, but lose their connections with the duct structures, invade diffusely the surrounding breast and produce widespread metastases, in the second variety, here described, the secreting tumor cells are apparently destroyed and only the duct carcinoma cells are responsible for the behavior of the tumor. It may be mentioned in this connection that Gillespie and Schmeisser described in one of their three tumors scattered epithelial elements separated by a loose stroma filled with mucin. There were solid nests of cells or definite gland formations. Some of the cells contained transparent droplets. Others were distended with mucinous material which pushed the nuclei aside, causing a signet ring appearance.

The intracystic papilloma with mucinous features is apparently not a malignant tumor but probably behaves as the transitional cell papilloma (Saphir and Parker). The benignity of these tumors was indicated by Geschickter, who stated that 19 of his 25 patients showing this tumor were traced. With the exception of 3 dying from other causes, all survived the 5 year period.

SUMMARY

This study reveals that mucinous carcinoma of the breast is not a single entity but can be classified into at least four definite types of tumors. The *true mucinous carcinoma* consists of duct or cystic structures filled with mucinous material in which groups of, or isolated, tumor cells may still be recognizable here and there. There are no other tumor structures present. This is apparently a rare tumor which clinically is relatively benign. The original conception of the benignity of these tumors must be traced to this variety of mucinous carcinoma of the breast. The *duct carcinoma with mucinous features* is the most common type. Areas similar to those seen in true mucinous carcinoma are intermingled with duct carcinomatous structures. Sometimes, however, these latter portions are seen only after sections of the whole breast have been examined. These tumors are just as malignant as simple duct carcinomas. The *signet ring cell mucinous carcinoma* is characterized histologically by well preserved mucin secreting cells with basophilic or clear cytoplasm and crescent shaped, compressed nuclei situated at the base of the cells. Whereas in the two former groups the secreting cells are soon destroyed, disappear, and large spaces filled with mucin remain, in the third group the signet ring tumor cells remain intact. Soon they become isolated from ducts and acini, invade the stroma and may produce the most widespread metastases, particularly in the ovaries. Though duct carcinomatous structures may also be present in this variety, the metastases consist mostly of signet ring shaped cancer cells. This tumor is regarded as highly malignant. Two patients died from widespread metastases soon after the detection of the primary tumor. Yet one patient is alive 4 years after operation. The fourth variety may be designated as *intracystic papilloma with mucinous features*. This is a relatively rare, nonmalignant tumor.

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THE ACCURACY OF ROENTGEN ESTIMATES OF PELVIC AND FETAL DIAMETERS

A. LOUIS DIPPEL, M.D., F.A.C.S., and E. DELFS, M.D., Baltimore, Maryland

MODERN roentgen pelvimetry and fetometry have been extensively developed during the past 6 years. As a result, they have been utilized by many hospitals and teaching institutions; in some, routinely in every primigravida and in every multipara with a previous history of difficult labor or delivery; and in others, only in selected cases, such cases being chosen for roentgen study after careful external and internal clinical mensuration and palpation. There are still, however, many obstetricians who do not utilize this valuable clinical aid. In some localities the number of definitely contracted pelves is relatively so small that roentgen pelvimetry is not often necessary and, under these circumstances, no urgent need is felt for the information obtained from roentgen pelvimetry and fetometry. Furthermore, there are many obstetricians who have not been convinced of the precision of these roentgen procedures. It cannot be said that these clinicians refuse to be convinced, but rather that those of us working in the field of obstetrical roentgenography have not placed sufficient importance upon the precision of our various techniques and have not emphasized the range of probable error in each. The main purpose of this paper is to attempt to evaluate the precision of several commonly employed roentgen methods of pelvimetry and fetometry.

The simplest technique, and the one most universally utilized in this country today, is the position method devised and perfected by Thoms (18–21), and modified by Torpin. Walton's method may be included here, since it depends upon essentially the same principles. The accuracy of the pelvic estimations from the inlet view, by these methods, is dependent solely upon the ability of the clinician or the x-ray technician to locate the plane of the pelvic inlet from external bony landmarks. As early as 1789, Baudelocque contended that the plane of the inlet lay in the plane located by the upper border of the symphysis pubis, anteriorly, and the depression beneath the spine of the fifth lumbar vertebra, posteriorly. It soon became evident to both anatomists and obstetricians that this was rarely the case, and roentgenologists have repeatedly shown that the posterior external landmark lies at a much lower level than the sacral promontory or even the projection of the iliopectineal lines on the sacrum. Accordingly, Thoms (21) has elevated the posterior external landmark until at present his technician marks the depression beneath the spine of the third lumbar vertebra. Torpin uses as the posterior endpoint the space lying between the spinous processes of the fourth and the fifth lumbar vertebrae.

It must not be forgotten that there is considerable individual variation in pelves and that often the plane of the pelvic inlet will not be located precisely from even these currently employed bony landmarks. However, Thoms (21) says that his "experiments with dried pelves have shown us that this posterior point may vary as much as 2.5 centimeters above or below the ideal situation, without measurably affecting the mensuration as recorded on the film." Since he measures to the nearest one-quarter of a centimeter on the film, it follows that his maximum error should be ± 2.5 millimeters, provided the anterior external landmark is correctly located and the posterior one is selected not more than 2.5 centimeters above or below the ideal location. The error under these circumstances can be mathematically proved to be not in excess of ± 2.1 per cent. The only means of determining the correctness by which these external landmarks are located is to observe the selected ones on the lateral film. Thoms (21) suggests that this lateral film could be taken first and developed before selecting the ideal location for the posterior external landmark. This should remove all doubt concerning the precision of the estimates made of the pelvis from its inlet view. Our own experience with the use of lead shot over the external landmarks, in 25 cases, has shown that such a step is necessary if the plane of the pelvic inlet is to be closely enough approximated by the plane of the external landmarks to keep the error consistently below 5 per cent. However, apparently without this precautionary step, Schumann measured the anteroposterior and transverse diameters of the pelvic inlet in a group of women,

From the Department of Obstetrics, Johns Hopkins University and Hospital.

both at laparotomy and from a roentgen inlet view made by Thoms' technique, and they came to the conclusion that the variation in length of each diameter, as determined by the two means, was constantly less than 2.0 millimeters.

The extent of error in the anteroposterior pelvic diameters, as determined from the Thoms' lateral roentgenogram, should amount only to that due to human error in applying a caliper length to a distorted centimeter scale, plus the probable error due to poor visualization of the endpoints of those diameters. This latter becomes a definite entity to be reckoned with when we deal with diameters extending to or from the lower margin of the symphysis pubis; the same is true of the ischial tuberosities, which, even with very good roentgen technique, are often not clearly outlined on the roentgenogram. Nevertheless, with accurate placing of the lead ruler and the production of a true lateral view of the pelvis, the precision by this method should reach a very high degree of accuracy in symmetrical pelves, for the intergluteal fold in all such cases probably lies in the sagittal plane of the pelvis. The same can be said of the lateral roentgenogram which is being developed by Hodges (12) and in which one-half the bitrochanteric diameter is used as the object-film distance.

The accuracy of roentgen cephalometry by the position methods mentioned leaves much to be desired. The precise determination of the distance between the geographical center of the fetal head, or between the endpoints of any fetal diameter, and the film, is the great source of error. Walton, however, has devised a unique method of checking the accuracy of his object-film distances. Lead markers are fixed to the anterior and to one lateral wall of the abdomen, over what is believed to be the geographical center of the fetal head, in each anteroposterior and lateral view. Both anteroposterior and lateral roentgenograms are taken without shifting the position of the patient from the supine. If the image of the radio-opaque marker appears at or near the geographical center of the fetal head, the previously recorded object-film distance can be used and accurate estimations of fetal head diameters anticipated.

Ball's method (1–3) has gained considerable popularity during the past few years and affords the minimum of mathematical manipulation. His present cephalometer (3) consists of a nomographic chart with a movable indicating member, which carries the calculations from the raw data immediately to the estimate of the length of the pelvic or fetal head diameter with one step.

The estimation, by the Ball method, of the object-film distance of any pelvic or fetal head diameter appearing, for instance, in the lateral view, is made from bony landmarks appearing in the anteroposterior view and includes the use of certain empiricisms. Thus, the object-film distance for the obstetrical conjugate diameter is estimated by measuring, on the anteroposterior film, the distance between the symphysis pubis and a point on the greater trochanter, to which must be added the table top to film distance. The point on the greater trochanter is a variable one and depends upon the tube-film distance used, being more laterally placed with greater tube-film distances. Ball believes that the distance between the point on the greater trochanter and the lateral surface of the thigh represents the amount of triangular distortion in the lateral film. He (3) has compared one-half the bitrochanteric diameter, as measured upon the patient, with the diameter obtained from bony landmarks, and has found that these correspond so closely that he believes arbitrary bony landmarks sufficiently accurate for practical purposes. However, in an earlier communication, he says that "the pelvic diameters are considered to be accurate to within 5 mm. The mean circumference of the fetal head is accurate to within 1 cm. in the majority of cases and 2 cm. in all cases." In a more recent article (2) he concludes that "in general it may be said that there has been a maximum error of 10 per cent in fetal head volume and 5 per cent in linear diameter measurements."

From time to time, since Varnier's work, in 1900, one investigator or another has rediscovered the idea that there is less distortion of an object when roentgenographed at a tube-film distance of 6 feet than at the more commonly employed tube-film distances, and has proposed that roentgenograms with the former technique represent undistorted radiography. Buchner has recently utilized this procedure in obstetrics, but we discuss the method only to indicate the relatively large radiographic distortion in teleoroentgenograms, and to show that they are neither "accurate" nor "record prenatal findings without bias." This can best be shown by similar triangles, as follows (Fig. 1.):

We let *FF* represent the film; *T*, the x-ray tube; *AB*, a pelvic diameter, which for convenience we assume measures 10 centimeters; and *HF*, an object-film distance of 16 centimeters, i.e., one-half the normal bitrochanteric diameter. The *a b* represents the projection of *AB* on *FF* when roentgenographed from a tube-film distance, *TF* of 6 feet (182.88 cm.), and *TH* represents the dis-

tance of the object below the x-ray tube (166.88 cm.).

From similar triangles:

$$AB : a\,b :: TH : TF$$

or, $10 : a\,b :: 166.88 : 182.88$

solving, $166.88\ ab = 1828.8$ cm.

$ab = 10.96$ cm.

But, 10 cm. = 100% of actual length of the object,
and, 10.96 cm. = 109.6% of actual length of the object,
or 0.96 cm. = 9.6% of actual length of the object.

Therefore, 9.6 per cent represents the amount of triangular distortion of a pelvic diameter in a lateral teleoroentgenogram. Thus it is seen that pelvic or fetal estimates from teleoroentgenograms are overestimated by essentially 10 per cent under normal pelvic conditions. Any haphazard position method, or even a rough guess at the object-film distance, would produce more accurate results. Moreover, much bony detail is sacrificed in reducing the amount of triangular distortion by increasing the tube-film distance.

All stereoscopic methods may be considered together, for they differ only in the instruments employed in working up the material. These methods have the advantage over the position methods that they require no positioning of the patient other than to show the pelvic diameters to best advantage, and their accuracy is not based upon the correct localization of external bony landmarks; nevertheless there are steps in procuring these roentgenograms which require precision. For instance, it is necessary to employ register or centering markers, so that when these, in each pair of stereoscopic films, are accurately superimposed, the result obtained is exactly the same as though both exposures had been made on a single negative. This can be accomplished with relative ease by adding permanent or removable markers to the casette carrier. Another equally important precaution is to employ the precise tube-film and tube-shift distances which are called for by the particular technique being used. Failure to observe the latter rule is probably the most common cause of technical errors in stereoscopic pelvimetry.

The ideal means of avoiding such errors would be the construction of a precise x-ray machine, such as the one in Hodges' (10) laboratory, for not only have the tube-film and tube-shift distances been precisely calibrated, but they can not be altered. If the technician then utilizes the total available tube-shift distances, there can be no question that these films are precise and estimations from them should be as nearly 100 per cent accurate as human error in interpreting them will allow. Unfortunately, no other x-ray laboratory has produced a similar precision x-ray machine and all other investigators have continued to utilize more or less non-precise x-ray machines. As a result, practically all these others have inserted into each pair of stereoscopic films, a radio-opaque marker of known length. The position of this marker is immaterial, the only requirement being that it appear in each film and that its position remain unchanged until both of a pair of stereoscopic films have been obtained. The chief point of interest lies in the attitude of various investigators toward this known marker.

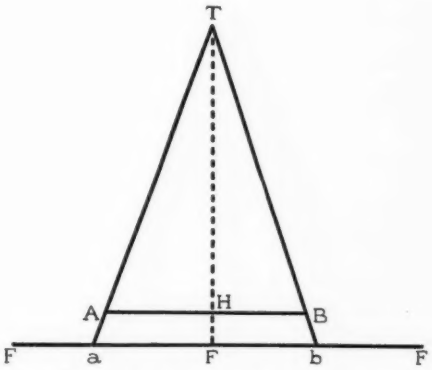

Fig. 1. Diagram indicating the distortion resulting from teleoroentgenography.

Clifford (6, 7) measures the control markers in each pair of films and says that if the method has been executed properly, the maximum error should be 0.2 centimeter; in other words, the maximum technical error should be ±2.0 per cent, for the control markers are actually 10 centimeters long. In those instances in which the technical error is greater, it has been customary at the Boston Lying-In Hospital to repeat the procedure, or to indicate that the results are not extremely reliable. Clifford reports an accuracy of within 3 millimeters in 97 per cent of the Class A films, i.e., those in which there has been no fetal head movement between or during the stereoscopic exposures. Since the classification of his films depends upon the presence or absence of evidence of fetal head movement, the accuracy of estimates of the pelvic diameters should be equally as good as the figures given, provided the endpoints are clearly visualized, for movement of the maternal pelvis between, or during, exposures is rare.

Johnson (13, 14) inserts a marker of known length into his stereoscopic films, but apparently does not measure its images routinely with his stereoroentgenometer. Since the basic principle

of stereoroentgenometry is sound, he does not consider it to be of great importance to establish the accuracy of his particular stereoscopic x-ray machine.

Although Caldwell and his co-workers are primarily interested in pelvic morphology, we find in the Moloy precision stereoscope (15, 16) not only a recognition of technical error, but also the first utilization of it. After inserting their anteroposterior films into the precision stereoscope, and before measuring the pelvic diameters with it, Moloy and Swenson (16) first measure the projected image of the known marker. If this measurement does not coincide with the known length of the marker, they alter the position of the optical system of the stereoscope and remeasure the image of the known marker. This procedure is continued until the measured length of the marker image coincides with its known length. By this procedure, the projected image of the pelvis should of necessity duplicate precisely the actual size of the pelvis. No statement on the accuracy of their estimates of pelvic diameters is made, since the accuracy is entirely dependent upon the experience of the observer with their stereoscope and upon his original stereoscopic sense.

During the development of the technique for the roentgen pelvimetry and fetometry studies at the Johns Hopkins Hospital, we realized the need of control markers of known length and some accounting of the technical errors, for the available x-ray machine was not precise. In each pair of stereoscopic films, the estimated length of the known marker was calculated by the graphic method of Hodges (10, 11). The deviation of this estimate above or below the known length of the marker was considered a positive or a negative technical error and its magnitude expressed in terms of percentage of the known length of the marker. At the same time, we were measuring the obstetrical conjugate diameter of the pelvis at the time of each laparotomy on the service. We noted, as was to be expected, that the smaller the roentgen technical error, the more closely the roentgen estimate of the diameter approached its actual length, as measured at operation. We then reasoned that we had been estimating the nature and the magnitude of the technical error from the marker of known length and that we should be able to correct all our original estimates of pelvic diameters to the extent of this technical error and produce estimates of the pelvic diameters which were of essentially 100 per cent accuracy. The following was the course of procedure:

Length of control marker images: 13.5 cm., 13.5 cm. } av. 13.5 cm.

Parallax shift: 4.25 cm., 4.25 cm. } av. 4.25 cm. Correction factor 0.705

13.5 cm. − 4.25 cm. = 9.52 cm.

But 10 cm. = 100% accuracy of technique (i.e., 10 cm. is the known length of marker)

and 9.52 cm. = 95.2% accuracy of technique

or 0.48 cm. = 4.8% accuracy of technique

∴ Technical error = −4.8%

And;

Length of obstetrical conjugate diameter images: 12.25 cm., 12.25 cm. } av. 12.25 cm.

Parallax shift: 3.3 cm., 3.3 cm. } av. 3.3 cm. Correction factor 0.754

12.25 cm. − 3.3 cm. = 9.25 cm.

But 95.2% accuracy of technique = 9.25 cm.

and 100% accuracy of technique = 9.72 cm.

∴ Corrected obstetrical conjugate diameter = 9.72 cm.

This procedure resulted in the corrected roentgen figure approaching the actual length of the pelvic diameter somewhat more closely than the uncorrected figure, but the corrected figure and the actual length of the pelvic diameter never coincided exactly. However, this procedure made it possible for us to report in an earlier paper (8) an average roentgen accuracy in measuring the obstetrical conjugate diameter of ±1.6 millimeters in 25 patients. Moreover, the technical error in each of these was never in excess of ±5 per cent. A further study of such comparative figures showed that negative technical errors resulted in overestimates of the pelvic diameters and positive technical errors in underestimates, the extent of the overestimate or underestimate depending upon the magnitude of the technical error.

The following mathematical procedures show a means of calculating the precise length of a pelvic diameter from the pair of stereoscopic films used for the mathematical calculations given, i.e., films produced by a non-precision x-ray machine and showing a definite technical error.

True length known marker = its image length x F (a correction factor).

Substituting available data 10.0 = 13.5 x F,

and, solving, F = 0.74, i.e., this correction factor applied to the image length of the known marker would give the true length of that marker, 10 cm.

Now, $F = \frac{K}{P + K}$ (21) where K = tube-shift distance and P = measured parallax-shift

Substituting, $0.74 = \frac{K}{4.25 + K}$

Solving, K = 12.1 cm., i.e., in obtaining the above pair of films a total tube-shift of 12.1 cm. was used

instead of 10.16 cm. We assume that essentially the correct tube-film distance, 91.44 cm., was used, since it is more easily measured with precision on the x-ray machine than the tube-shift distance and since errors in tube-film distance do not produce as great technical errors as do errors in total tube-shift distance.

Then, solving for the true length of the obstetrical conjugate

as above, $F = \frac{K}{P + K}$

Substituting, $F = \frac{12.1}{3.3 + 12.1}$

Solving, $F = 0.786$ (correction factor for the obstetrical conjugate images obtained from the actually employed roentgen technique.)

Furthermore:

True length of obstetrical conjugate = its image length x F
$= 12.25 \times 0.786$
$= 9.62$

This obstetrical conjugate actually measured 9.6 cm. at laparotomy and this estimate is much more precise than the uncorrected roentgen figure, even more precise than the corrected estimate for it.

Thus, it is seen that it is possible to obtain precise estimations of pelvic diameters by this means of utilizing the marker of known length and from its images calculating the actual tube-shift distance used by a non-precision x-ray machine. The overestimate of the pelvic diameter from a use of the magnitude and nature of the technical error was not great. However, longer diameters at greater object-film distances have been found to result in errors amounting to more than 6.0 millimeters when calculated by the use of the technical error. This is true since the curve for triangular distortion correction factors is not a straight line, and this fact also explains why the use of the technical error method of correction does not result in precise estimations of pelvic or fetal diameters. If the curve were in reality a straight line, the latter procedure would be mathematically sound.

By comparing the estimate of a pelvic diameter obtained by the precision method described (i.e., by calculating from the known marker images, the actual tube-shift distance employed and then determining the correction factor for this tube-shift and the tube-film distance) with the uncorrected and corrected estimates of the same diameter as obtained by the application of the technical error, we have noted a strikingly close approximation of the average of these last two estimates to the former. These approximations are shown in the appended table. It is, therefore, shown that the shorter mathematical procedure represented by the use of the technical error method can be used and will produce remarkably precise estimates of pelvic and fetal diameters.

An immediate objection to the last described methods will be that they entail considerable mathematical manipulation. This is, of course, true, but such mathematics is usually simple arithmetic, never more complicated than high school algebra. Furthermore, if we expect to attain precision, it will probably not be accomplished through great simplicity. We do not propose that it should be necessary to go through a lengthy mathematical procedure routinely for every available pelvic or fetal diameter, in every pair of stereoscopic films. What we do wish to emphasize, however, is the need for determining the technical error in every pair of stereoscopic roentgenograms obtained by a non-precision x-ray machine and the utilization of this error, when it is a sizable one, in cases of borderline pelvic contraction. Only in such a manner will it be possible to furnish precise estimates of maternal pelvic or fetal diameters in cases in which precision will definitely indicate a choice between spontaneous delivery or a more radical elective procedure.

Recently, Friedman and Euphrat have published a preliminary report of a parallax method based upon principles originally described by Hodges and Ledoux (10). The results obtained with this method were highly accurate in measuring a dried pelvis. They have demonstrated that some mathematical manipulation may be avoided and extremely accurate pelvic estimates obtained by simply locating the footpoints of the target from its respective stereoscopic positions and utilizing these. It would seem that this should be a relatively simple and highly accurate method for diameters which are parallel to the film, provided the footpoints can be accurately located. This latter task may necessitate some calibration of the x-ray machine, if precision is to be consistently obtained. Moreover, the calculation of diameters which are not parallel to the film will require additional but simple mathematical procedure, as well as some precise knowledge of tube-film and tube-shift distances. However, this method offers valuable possibilities for the accurate determination of most of the important obstetrical diameters from stereoscopic films which are produced by the average roentgen-ray equipment.

During the past 5 years, we have primarily employed the Hodges graphic method, with the modifications described, to obtain more precise end-results than were otherwise possible with the nonprecision x-ray machine at our disposal. During the past year, we have occasionally resorted

Fig. 2. Photograph of precision caliper used in measuring pelvic diameter at the time of laparotomy. It is made of two cylinders, one telescoping into the other on a screw, and is calibrated in one-tenths of a millimeter. The surface of one end is slightly curved, so that it will fit snugly on the sacral promontory when measuring the obstetrical conjugate. The curved plate on the outer cylinder is for purposes of grasping and holding the instrument between the fingers of one hand while the other hand is used to screw the inner cylinder in or out until the instrument fits snugly between the endpoints of the pelvic diameter.

to the precision method for the calculation of extremely important pelvic diameters in cases of cephalopelvic disproportion or markedly contracted pelves. Also, in search of simpler yet precise technical and mathematical methods, we have tried several other methods in current use in this country. Finally, a series of patients were measured by these several methods and certain actual pelvic measurements obtained with a precise caliper (Fig. 2) at laparotomy; museum specimens of bony pelves were similarly studied. Table I shows a few comparative estimates and measurements of obstetrical conjugate diameter.

It has been our experience that the technical difficulties with mensuration of pelvic diameters at laparotomy are great, in spite of the use of a precision instrument and even on a diameter with as definite endpoints as the obstetrical conjugate. In our opinion, it is for this reason that roentgen estimates of a pelvic diameter more closely approach the actual measurement on a museum specimen of a pelvis than on the living subject at laparotomy.

In Table I, the "Hodges graphic" method indicates our own modifications of his original method. We consider the average figures from this method to be the most precise from any method we have thus far used with a nonprecise x-ray machine, except possibly for the "precision" method. We have continued to use the former, since pelvic diameters may be estimated from a previously calculated table of triangular distortion correction factors, thus eliminating the necessity for calculating the correction factor for each diameter to be estimated. Our stereoroentgenometer is of the Hodges (11) type and furnishes highly accurate estimates when the technical error is small. However, when these errors are large, we can not expect a high degree of accuracy, for the stereoroentgenometer is set for the roentgen technique *supposed* to have been employed in obtaining the stereoscopic films. Yet, as is shown in the table, the end-results are quite accurate when we utilize the technical error method of correction, as in the case of the graphic method and obtain the average between corrected and uncorrected estimates. Furthermore, as will be seen in the table, the corrected figures are overestimates to almost exactly the same degree as the uncorrected figures are underestimates, quite irrespective of the method of mensuration of the nonprecise stereoscopic films. The "footpoint" method is essentially the same as that described by Friedman and Euphrat, except that the target footpoints were located by means of a simple device developed in Hodges' laboratory and is a method which requires no precise knowledge of the x-ray factors employed in obtaining the stereoscopic films except for the tube-film distance. Further precise information is, of course, necessary in this method only when the pelvic diameter to be measured lies at an angle to the film.

TABLE I.—ESTIMATES OF THE LENGTH OF THE OBSTETRICAL CONJUGATE[1]

Subject of study	Methods employed, with resultant estimates and direct measurement of obstetrical conjugate									
	Hodges' graphic			Precision	Stereoroentgenometer			Footpoint	Thoms' lateral	Direct measurement
	Uncorrected	Corrected	Average		Uncorrected	Corrected	Average			
Pelvis A.	9.11	9.72	9.46	9.43	9.65	10.27	9.96	9.20	—	9.60
Pelvis B.	8.74	9.96	9.35	9.42	8.80	10.11	9.45	10.05	—	9.40
Patient L. J.	11.89	12.11	12.00	12.00	11.85	12.03	11.94	17.00	12.45	11.45
Patient I. R.	10.72	11.25	10.99	11.02	10.65	11.21	10.93	10.90	10.90	10.93
Patient E. M.	10.51	10.86	10.68	10.69	10.50	10.76	10.63	11.35	10.70	10.30
Patient T. W.	11.40	12.10	11.75	11.81	11.50	11.98	11.74	11.20	11.46	11.85

[1]Obtained from several roentgen methods compared with the direct measurement obtained from two museum specimens of bony pelves and from our patients at the time of laparotomy.

The end-results obtained by this method are generally quite accurate and with further experience, such inaccuracies as shown under patient L. J., can be avoided. An error was anticipated in this case, since the footpoints fell very near to the longitudinal plane of the pelvis. As a rule, the estimates from the "Thoms lateral" view were quite accurate. Our errors with this method have undoubtedly resulted from not placing the lead ruler in the median plane of the pelvis. Such errors were usually avoided by the "Hodges lateral" method (not shown in the table), in which one-half the clinical bitrochanteric measurement is used as the object-film distance. However, it is true that both of these latter two methods will produce errors in certain asymmetrical pelves.

Results from lateral pelvimetry alone have been recorded here, although quite similar results were obtained in these subjects from anteroposterior pelvimetry. The true endpoints of the greatest transverse diameter of the inlet are more difficult to make out, both on roentgenograms and at operation, than those of the obstetrical conjugate in the lateral view, and hence transverse measurements do not lend themselves as readily to comparisons. However, good results were obtained with the Hodges graphic, precision, and stereoroentgenometer methods, when used as for the lateral view. The accuracy of the footpoint method varied somewhat, aside from the occasional incorrect lateral placement of the target footpoints. The results with the Thoms inlet view varied directly with the precision by which the posterior external endpoint of the pelvic inlet could be located.

SUMMARY

1. A plea is made for concrete evidence by each investigator of the accuracy of roentgen estimates of pelvic and fetal diameters, as compared with easily measurable diameters on museum specimens or obstetrical patients at laparotomy. General knowledge of their accuracy should increase the utilization of such valuable prenatal aids as roentgen pelvimetry and cephalometry.

2. Each of the popular methods of obstetrical roentgen mensuration has an accuracy which is generally adequate for clinical purposes.

3. Two mathematical procedures for the production of precise estimates from stereoscopic films taken by a nonprecision x-ray machine, are given.

4. In our hands, the Hodges graphic, the precision, and the stereoroentgenometric methods have proved almost equally good in the production of precise estimates of maternal pelvic and fetal diameters. The footpoint method has shown variations in precision but has very definite possibilities. The Thoms and the Hodges lateral methods for measurement of anteroposterior pelvic diameters are generally quite accurate, but correct placement of the lead ruler in the former is highly essential to precision, and pelvic asymmetry precludes consistent precision with either method. The Thoms inlet view has furnished us with precise estimates of transverse pelvic diameters only when we have been fortunate in approximating the level of the pelvic inlet in the selection of the posterior external bony landmark.

We acknowledge with gratitude our indebtedness to Dr. Paul C. Hodges for valuable aid and suggestions throughout our studies in obstetrical roentgenography. The close co-operation of the Division of Roentgenology of the Johns Hopkins Hospital, and especially that of Mr. James C. Fletcher, its chief technician, has made it possible for us to employ several roentgen techniques and to prove the accuracy of each.

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CONSTRICTIVE OCCLUSION OF THE SUPERIOR VENA CAVA

Report of Three Cases in Which the Patients Were Treated Surgically

HOWARD K. GRAY, M.D., F.A.C.S., and IRA C. SKINNER, M.D., Rochester, Minnesota

CONSTRICTIVE occlusion of the superior vena cava with or without accompanying thrombosis of the vessel is fortunately a very rare occurrence. Ochsner and Dixon, in 1936, after an exhaustive study of the world literature, were able to collect only 120 cases of thrombosis of the superior vena cava. Erlich, Ballon, and Graham, in 1934, found only 309 cases of all types of obstruction to the superior vena cava. Hinshaw and Rutledge have recently added to this list 20 cases in which the patients were examined personally by them at the Mayo Clinic. The causation of the occlusion in 4 of their cases was thought to be constriction of the vessel, with associated thrombosis resulting from inflammatory changes in the mediastinum.

The collected cases of thrombosis of the superior vena cava have been classified by Ochsner and Dixon as to causation in the following manner: 44, 36.6 per cent, resulted from phlebitis; 35, 29.1 per cent, from external compression; 28, 29.1 per cent, from mediastinitis; and in 13, 10.8 per cent, the cause either was not stated or was unknown. Of the 44 cases of phlebitis and associated thrombosis, 20 were classified as idiopathic, 10 were associated with cardiac disease, 12 were cases of syphilitic phlebitis, 4 were tuberculous phlebitis, 7 were pyogenic phlebitis and 1 was traumatic phlebitis. External compression was thought to be the cause of thrombosis in 35 cases. Of these 35, 18 were associated with mediastinal neoplasms and the remainder with aneurysms. Of the 28 cases in which there was antecedent mediastinitis, syphilis was the etiological agent in 11 cases, tuberculosis in 10 cases, trauma in 1 case, and in 5 the causation of the mediastinitis was unknown. The underlying etiological agents named in order of their frequency in the production of thrombosis of the superior vena cava in the reported cases are: syphilis, tuberculosis, cardiac disease, pyogenic infections, and trauma.

The average age of the patients in the reported cases was 43.6 years. The disease occurred approximately twice as frequently among male patients as among female patients.

From the Division of Surgery, the Mayo Clinic and the Department of Surgery, the Mayo Foundation.

As a result of occlusion of the superior vena cava, a marked increase in the venous pressure in the upper half of the body occurs, with the production of a characteristic clinical picture. Edema of the face, neck, and upper extremities becomes a distressing feature. At the onset of the condition the edema may be intermittent. It decreases after the patient has been up and around and is aggravated by the recumbent position. Exercise and bending forward on the part of the patient exaggerate the edema. Edema of the eyelids may be an early sign of the disease. Sudden death has been attributed to edema of the glottis by Rauth. Cyanosis, particularly of the lips and lobes of the ears, may be a prominent feature. Suffusion of the conjunctival vessels and dilatation of the retinal veins on funduscopic examination are again evidence of venous stasis. Dyspnea, occurring as a result of chemical changes in the blood, is present early. Stasis in the cerebral vessels results in congestion of the cerebrum and increased pressure of the cerebrospinal fluid. Headache may be the presenting symptom. In one of our patients typical jacksonian epilepsy developed, as occurred also in the case reported by Chiray and Semelaique. In Samek's case, psychosis developed. Other symptoms, such as vertigo, somnolence, deafness, tinnitus, epistaxis and visceral disturbances, have been reported. Pleural effusion may occur. Occlusion of the superior vena cava manifests itself objectively in increased venous pressure, collateral diversion of the blood stream, and delayed circulation time. Fischer has divided obstructions into three anatomical types together with the number of times each type occurred: (1) obstruction below the orifice of the azygos veins, 31 of 166 cases; (2) obstruction including the azygos veins, 121 of 166 cases; (3) obstruction above the orifice of the azygos veins, 14 of 166 cases. Carlson (3) demonstrated experimentally in dogs that obstruction of the superior vena cava above the azygos veins was well tolerated, whereas obstruction below those veins was fatal for the 2 animals in which it was attempted. Occlusion of the azygos system and superior vena cava could be successfully accomplished if carried out in two stages. Carlson found that an early return to relatively normal

venous pressure occurred in dogs in which obstruction had been accomplished above the orifice of the azygos veins, whereas in those with occlusion of both vena cava and azygos vein, high venous pressure was maintained for long periods.

The collateral circulation, following occlusion of the superior vena cava, has been described by various investigators, such as Hallett, Fischer, Carlson (3), Blasingame, and Hinshaw and Rutledge and others. On the development of an efficient collateral circulation depends the future health of the patient and his ability to return to a gainful occupation. The anastomotic route utilized is determined largely by the situation of the occlusion, as has been brought out by Carlson. The systems available for shunting the blood around the obstructing lesion in the vena cava may be divided into a superficial system and a deep system. The superficial veins include the thoraco-epigastric, superficial epigastric, and the superficial plexus of veins of the thorax and abdomen, and the deep veins involved are: the internal mammary, azygos, hemiazygos, accessory hemiazygos, anterior and posterior mediastinal, intercostal, pericardiophrenic, phrenic, superior and inferior epigastric, lumbar, and deep veins of the back. Carlson (2) demonstrated experimentally in dogs that when obstruction above the junction of the vena cava with the azygos vein occurred, the azygos system was a very important path for the return flow of blood to the heart and that the abdominal collateral vessels were not well developed. In the presence of obstruction, including the azygos vein, the flow of blood in the remainder of the azygos system is evidently reversed and the superficial and deep abdominal collateral vessels carrying blood to the femoral and iliac veins or to the inferior vena cava are therefore much more prominent than normally.

Study of the collateral channels developed will enable the surgeon to localize the obstruction in a large percentage of cases, as has been emphasized by Hinshaw and Rutledge. They stated that in the presence of obstruction occurring above the level of the orifice of the azygos veins, a marked plexus of large veins may be seen over the sternum, often clearly connecting with the perforating branches of the internal mammary vein. It is apparent that the blood is seeking a route to the intercostal vessels and thence to the azygos system. Since this is a relatively efficient route of communication, venous pressures are not so high and symptoms not so severe as in the instances in which other routes are necessary.

If the superior vena cava and its azygos tributaries are obstructed, it becomes necessary for the blood from the upper half of the body to be returned to the heart through the inferior vena cava. In patients who have such obstruction, large dilated vessels are seen extending from the thorax to the lower parts of the abdomen and groin. There is a reversal of the flow of blood in these vessels which is easily demonstrable. The blood in a segment of vein is pressed out, and both ends of the segment are compressed by the index fingers. Release of the lower finger causes the vein to fill slowly or not at all, whereas on release of the upper finger the vein refills almost instantly. Since this collateral route to the inferior vena cava is long and difficult, venous pressures are high and symptoms are marked. Occlusion of the superior vena cava below the termination of the azygos system manifests itself clinically in a similar way.

Hinshaw and Rutledge have called attention to the value of thorough inspection of the thorax for those patients suspected of having mediastinal lesions. They have noted small, superficial, very tortuous groups of dilated venules which make their appearance along the anterior costochondral margins of patients who have obstructing lesions within the mediastinum. These differ in appearance from the large dilated varicosities seen over the thoracic wall, and may be the first objective signs of mediastinal disease; hence, their great clinical importance. Their presence is sufficient indication for a thorough roentgenological study of the thoracic cavity.

Laboratory aids in the diagnosis include estimations of direct venous pressure, determinations of the circulation time, and, of course, roentgenograms of the thorax. It is particularly important to follow the direct venous pressure of these patients for whom surgical intervention is contemplated. We believe that only those individuals who show progressive increases in their venous pressures over a period should be subjected to mediastinotomy. The circulation time, as measured by the dehydrocholic acid (decholin) method, will be found to be prolonged in the presence of obstruction of the superior vena cava, because the blood is compelled to take a circuitous route in its return to the heart. The value of making roentgenograms of the thorax need not be mentioned.

We are again indebted to Ochsner and Dixon's excellent review of the literature for the mortality figures for patients suffering from thrombosis of the superior vena cava. Of the 120 collected cases, 85 patients died. In those cases in which thrombosis of the superior vena cava was caused by aneurysm, the mortality rate was 73.3 per cent; in those in which the condition was

associated with neoplasia, the rate was 94.4 per cent and in 24 cases those in which mediastinitis was present, 22 patients died. Of the 44 patients who had phlebitis, 32 died. In addition to this terrific mortality it is probable that those patients who survived were incapacitated for long periods. As is evident, the prognosis is dependent to a large degree on the etiological agent causing the thrombosis. Until relatively recently, there has been very little in the way of treatment to offer these unfortunate people. Phlebotomy with removal of several hundred cubic centimeters of blood may be temporarily beneficial. Antisyphilitic therapy is of great value for those patients who have syphilitic endophlebitis or mediastinitis. Roentgen therapy is of no benefit unless an associated radiosensitive tumor is present. Skillern, in 1917, made the suggestion that decompression of the thorax might be of some benefit in those cases in which there was increased intrathoracic pressure, resulting, for example, from a neoplasm or aneurysm. Ehrlich, Ballon, and Graham reported a case in which mediastinal decompression aided a patient suffering from superior vena caval obstruction caused by mediastinal Hodgkin's disease. The patient operated on by Ochsner and Dixon derived great benefit from the separation of adhesive bands surrounding the thrombotic superior vena cava. We wish to report 3 cases in which the patients have been operated on at the Mayo Clinic recently. Two of these had what was believed to be thrombosis associated with constricting bands, and the third had only constriction as a result of tuberculous mediastinal glands.

One case (Case 2) has been reported previously by Rutledge and Gray. It is repeated herein for the sake of completeness, since additional follow-up notes have been made.

REPORT OF CASES

CASE 1. A housewife, aged 37 years, came to the clinic in May, 1939. She had been perfectly well until the onset of her present illness, except for injuries sustained in a minor automobile accident in November, 1937. At that time she had received a slight contusion of the anterior thoracic wall which inconvenienced her for only one day. In September, 1938, she had begun to complain of a sensation of fullness in her throat and a slight swelling of the face. The symptoms were exaggerated by exercise and by bending forward. She gradually became worse and was unable to sleep, unless she was propped up on two or three pillows, because of the sensation of tightness in her thorax and throat. Dyspnea and a mild degree of cyanosis made their appearance. Three months prior to her admission to the clinic she had noted that the veins of her chest, arms, and face were becoming more prominent.

On physical examination edema (graded 3 on the basis of 1 to 4) of the eyelids, neck, and upper extremities was found to be present. The veins of the thorax were dilated and prominent as were the venules along the anterior costochondral margin (Fig. 1). A soft enlarged node was palpable in the left axilla. Roentgenologic examination of the thorax revealed a shadow on the right, above the arch of the aorta, which was interpreted as being an accentuation of the shadow cast by the vena cava. The direct venous pressure in the right arm was 336 millimeters of water and in the left, 330 millimeters. The remainder of the physical examination and laboratory tests revealed no abnormal findings.

A clinical diagnosis of superior vena caval obstruction probably associated with mediastinal fibrosis was made.

It seemed advisable to secure a specimen of the enlarged node in the left axilla for biopsy before mediastinal exploration was undertaken. On May 5, 1939, the node was removed through a small incision in the left axilla. The pathologist reported it to be an inflammatory lymph node.

On May 23, 1939, exploratory mediastinotomy was carried out under anesthesia produced intratracheally with gas and ether. Exposure was accomplished by the usual U-shaped incision, the right breast being reflected upward and medially. The pectoralis major muscle was cut across over the third interspace anteriorly, the pleural space opened and the ribs were reflected with the retractor. A hard tumor-like structure could be felt in the region of the superior vena cava, through the mediastinal pleura. This started just proximal to where the superior vena cava dipped behind the pericardial fold and extended upward for approximately 4.5 centimeters; it was roughly 2.5 centimeters in diameter and almost bone-hard in its consistency. More definite exposure being obtained by incising the mediastinal pleura, a band-like structure was observed which seemed to be constricting the vena cava. This was split longitudinally to a depth of approximately 3 millimeters, and a portion was sent to the laboratory for histopathological examination. It did not seem advisable to carry the dissection further, lest uncontrollable hemorrhage result. Anatomical closure of the incision was accomplished after reinflation of the lung. The tissue which was removed proved to be fibrous inflammatory tissue. A transfusion of 500 cubic centimeters of citrated blood was administered slowly during the operation.

Immediately after operation the patient was placed in an oxygen tent, where she remained for 4 days. Roentgenological and physical examination of the thorax on May 31, 1939, showed evidence of the presence of fluid in the base of the right lung. However, as the fluid was thought to be of small amount and as the patient was having no respiratory difficulties, thoracentesis was not performed. Determinations of direct venous pressure on May 27 and April 6 were 250 millimeters of water. The patient progressed unusually well and was dismissed from the hospital on the seventeenth postoperative day. She left for her home, a distance of approximately 800 miles, on the twenty-first postoperative day.

Her referring physician was kind enough to keep us informed as to her subsequent progress. On July 14, 1939, he found her venous pressure to be 240 millimeters of water and on July 17, 253 millimeters. She had only a slight remaining fullness of the face and was able to lie flat in bed without the choking sensation which had been her chief complaint. The patient wrote that she was "beginning to feel like her old self again."

CASE 2. The patient, a coal miner, aged 27 years, first registered at the clinic in January, 1939. He complained of swelling and flushing of the face which had been noticeable for about 14 months. He had had several attacks of pneumonia before he was 11 years of age. He stated that on November 11, 1937, he had suddenly noticed that if he used his arms actively or stooped, his face became flushed

and swollen. At first these symptoms subsided shortly after he stopped such activity, but within a month they seemed to be present continuously. When he attempted to work, the swelling increased and he noticed a bluish discoloration of the face and neck. In April, 1938, he first noticed enlargement of the veins of his neck, chest, and arms. These had continued to enlarge to the time of his admission. In December, 1938, the patient had to stop work because of a sensation of choking when he attempted to do anything strenuous. Edema of the lower extremities had not been present and he had no other complaints.

On physical examination at the clinic the patient's face and neck appeared to be flushed and swollen. Slight activity, such as bending over several times, aggravated the symptoms. There was marked dilatation of the veins of his chest, arms, neck (Fig. 2) and especially of the angular veins of the face. The direction of blood flow in the veins was toward the umbilicus. The clinical observations referable to the heart were not remarkable. Roentgenological examination of the thorax revealed evidence of slight thickening of the soft tissue about the vertebrae on the left side and exaggerated pulmonary markings, but did not reveal any calcification of the pericardium. The electrocardiographic tracing was that of a normal heart. The direct venous pressure in the right arm was 335 millimeters of water and in the left, 345 millimeters. Normal venous pressure is between 40 and 120 millimeters of water. The pulmonary circulation time, measured after the administration of a dehydrocholic acid preparation (decholin), was 29 seconds. The average normal time is about 14 seconds. Results of other laboratory tests were negative.

It was believed that the patient was suffering from obstruction of the superior vena cava between the azygos vein and the entrance of the vena cava into the right auricle, possibly a postinflammatory condition. Roentgen therapy was given, and the patient was sent home for one month.

On his return on February 13, 1939, the patient stated that his condition was about the same, but that in addition to the previously mentioned complaints, he had had three attacks of severe jerking movements of the left arm and leg which had lasted about one minute each. He did not lose consciousness when these episodes occurred. Roentgenological examination of the skull and examination of the eyes with a funduscope revealed nothing abnormal. On neurological consultation the attacks were thought to be jacksonian seizures which probably had a vascular basis. The direct venous pressure in the right arm was 424, in the left, 416. and in the right ankle, 102 expressed in millimeters of water. After consultation, it was decided that in view of the progression of the condition, the patient was entitled to surgical exploration.

Exposure was accomplished by making an incision from the upper portion of the anterior axillary line to the suprasternal notch (Fig. 3). The skin and subcutaneous tissue overlying the right pectoralis major muscle was deflected upward and down on the line between the two points, and a linear incision was made across the pectoralis major muscle over the third rib and cartilage. The medial point of the incision through the muscle was then carried downward for approximately 3 inches (7.6 centimeters) along a line which was about 1 inch (2.5 centimeters) from the insertion of the muscle. The triangular pieces of muscle were then reflected downward and outward and approximately 11 centimeters of the third rib, together with approximately 3 centimeters of the costosternal cartilage of this rib, was removed. The cartilages of the second and fourth ribs were divided to permit greater exposure and dissection was then carried down to the pleura. The pleura was reflected laterally and extrapleural exposure of the mediastinal structures was accomplished with some difficulty, because of the presence of a moderate quantity of fibrous tissue in this region. A small rent in the pleura allowed the right lung to collapse, and greater visualization of the mediastinal structures was obtained. Beginning about 2.5 centimeters above the pericardial reflection, there was an extremely hard tumor within the lumen of the superior vena cava, approximately 3 centimeters in its longest diameter; the lowermost portion of this lesion extended beneath the pericardium. Evidence of extraluminal tumefaction was not found. An elongated constricting band, approximately 2 centimeters in width, which compressed the superior vena cava, was divided so that the vena cava dilated at the point of previous constriction (Fig. 3). A small lymph node from the tissue immediately adjacent was removed and sent to the pathological laboratory for histopathological examination. It was found to be inflammatory. A small portion of the constricting band was removed and this also was found to be inflammatory tissue. Because the obstructing process was entirely within the superior vena cava and could not be removed, it was thought best to discontinue the exploration. The small rent in the pleura was closed, the right lung reinflated by means of positive pressure, and anatomical closure of the wound was accomplished.

For the first 5 days immediately after the operation there was considerable swelling of all of the soft tissues of the upper portion of the thorax, neck, and arms; particularly the tissues of the left arm. This was so marked that it was impossible for the patient to flex the left arm. The venous pressure in the left arm during this period was higher than any pressure the manometer could register, that is more than 500 millimeters of water. After the first week the swelling gradually subsided and the pressure within the veins of the arm decreased concomitantly. At the time of the patient's dismissal from the clinic, which happened on the thirty-second postoperative day, direct venous pressure of the arm had decreased to 290 millimeters of water. The veins on the upper portion of the thorax were much less prominent and in general the patient had remarkably improved.

The patient returned to the clinic for re-examination in June, 1939, as had been requested of him. His improvement had continued and for a month he had been able to return to a somewhat less strenuous job at the coal mine. He had experienced no more jacksonian seizures and was practically free of edema of the face and arms except after rather marked exertion and bending forward. The direct venous pressure in the right arm measured 278 millimeters of water. This patient was considered to have achieved an excellent functional result.

CASE 3. A mechanic, aged 32 years, was first seen at the clinic in March, 1939. He stated that for the past 9 months there had been intermittent swelling of his face, neck, and arms, occurring after exertion. Cyanosis of the lips, lobes of the ears, and fingernails would accompany the edema. The symptoms were relieved by rest and they had not progressed much in severity. At times the attacks were accompanied by hoarseness and dyspnea. The patient's physician at home had made a presumptive diagnosis of obstruction of the superior vena cava and had removed a gland from the left axilla which proved to be inflammatory in nature.

On physical examination, a slight degree of edema of the face and neck was noted. After the patient had exercised, the edema became much more marked, and distention of the right and left external jugular and right and left cephalic veins became very apparent (Fig. 4). No abnormal structures could be visualized in the mediastinum on roentgenological examination. The venous pressures in the

Fig. 1. Case 1. Infra-red photograph showing marked tortuosity of the superficial veins of the neck and thorax.

veins of the right and left arms were, respectively, 294 and 276 millimeters of water, whereas the pressure in the left greater saphenous vein measured only 48 millimeters of water. Reactions to the flocculation test for syphilis were negative. Results of other routine laboratory tests added nothing of interest.

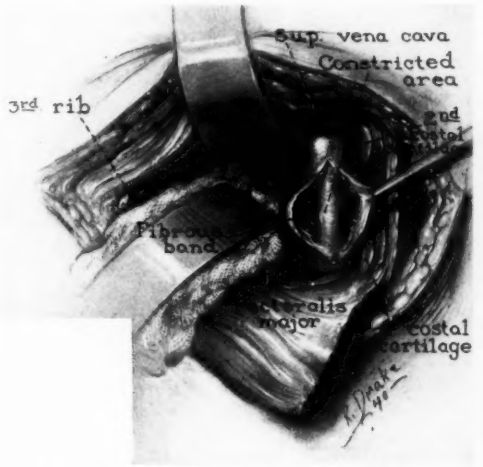

Fig. 3. Artist's conception of the release of an inflammatory constricting process which had practically completely occluded the lumen of the superior vena cava below the orifice of the azygos veins. The constricted area has been released by separating the fibrous band. A U-shaped incision beneath the breast may give better exposure and cosmetic results than that shown by artist.

Fig. 2. Case 2. Infra-red photograph showing marked dilatation and tortuosity of the veins of the chest, arm, and neck.

The diagnosis of incomplete superior vena caval obstruction was made. It seemed best to follow the patient's progress a short time by means of determinations of venous pressure, since there had not been much progression of the symptoms since their onset.

The patient returned to the clinic within one month, as had been requested of him. His symptoms had definitely progressed and one week before his return he had had an acute episode of edema. His collar size had increased from 14½ to 16¼ inches (35 to 40 centimeters). The direct venous pressures in both the right and left arms were 394 millimeters of water. Because of the progression of symptoms it was deemed advisable to explore the region of the superior vena cava.

Fig. 4. Case 3. Infra-red photograph showing the distention of the right and left external jugular and right and left cephalic veins, together with generalized venous tortuosity.

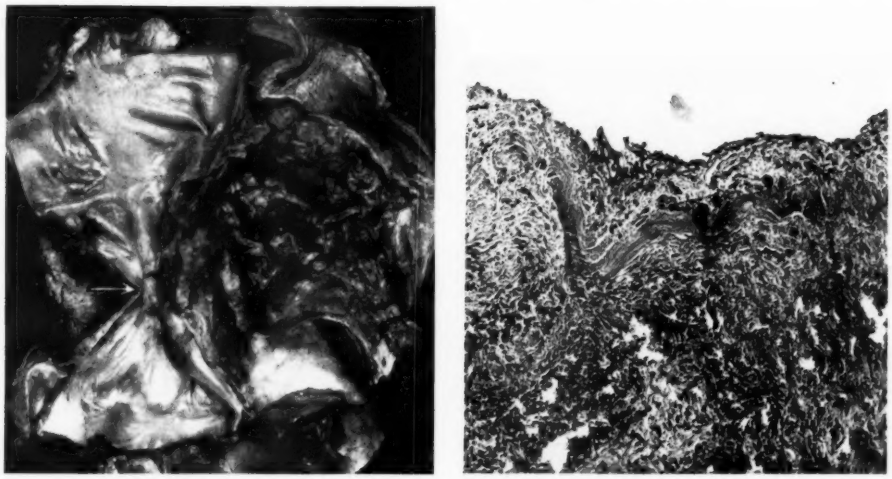

Fig. 5. Constriction of superior vena cava by a mass of calcified tuberculous lymph nodes; *a*, left, arrow points to portion of vena cava constricted; *b*, section of tuberculous mediastinal lymph node. Hematoxylin and eosin stain ×100.

On May 3, 1939, mediastinotomy was performed under gas-ether anesthesia supplemented by pentothal sodium given intravenously. Exposure was accomplished through the usual incision. A hard tumor, approximately 3 centimeters in length, was found in the region of the superior vena cava, proximal to the pericardium. On further dissection it was found that the parietal pleura was densely adherent to this, as were the other surrounding structures. These were dissected free with extreme difficulty, and a constricting mass, stone hard in nature was noted. This mass was split end-to-end on each side so as to release the constriction at this point. It could not be definitely determined whether there was thrombosis within the vein or whether the mass was entirely extraluminal. A lymph node from the adjacent region was sent to the laboratory and found to be an inflammatory node. A small portion of the stone-hard, constricting mass proved also to be inflammatory tissue on microscopic examination. During the dissection a moderate amount of hemorrhage was encountered. Plastic closure of the wound was accomplished.

On the second postoperative day the patient suffered rather severe shock and succumbed.

On postmortem examination the superior vena cava was found to be occluded to approximately 80 per cent of its normal size by pressure caused by a mass of calcified tuberculous lymph nodes (Fig. 5a and b). The other anatomical diagnoses were: healed tuberculosis of the liver and spleen, accessory pancreas of the pylorus, postmortem autolysis of the cardia of the stomach, adenoma of the adrenal glands, arteriosclerosis (graded 1, on the basis of 1 to 4), hemorrhagic edema of the lungs with bronchopneumonia, diverticulum of the sigmoid and hemorrhage (300 cubic centimeters) into the right pleural cavity.

It is of interest to consider the causation of the obstruction in the cases just presented. Causation of the thrombosis in the first case is not definitely known. It seems hardly probable that the minor injuries of the thorax which the patient sustained a year previous to the onset of her symptoms could have been the cause of the mediastinal fibrosis and the thrombosis of the vena cava. It is more likely that this patient at some time had experienced tuberculosis of the mediastinal lymph nodes or nonspecific mediastinitis.

It would appear that the second patient had mediastinitis accompanying one or more of his attacks of so called pneumonia, with resulting fibrosis within the mediastinum and thrombosis of the superior vena cava.

On postmortem examination it was discovered that the third patient had suffered from compression of the superior vena cava by calcified tuberculous lymph nodes, without accompanying thrombosis.

It is also of interest to speculate as to why the release of constricting bands should result in clinical benefit in those cases in which definite thrombosis occurs within the lumen of the vena cava. Duval was of the opinion that removal of the constricting perivenous tissue permits opening of the already canalized channels within the thrombus, these vessels having been previously maintained as nonfunctioning canals because of the external pressure exerted by the encapsulating perivascular cicatricial tissue.

SUMMARY

Three cases of constrictive occlusion of the superior vena cava in which the patients were treated by operation have been reported. In 2 of

these there was probably an associated thrombosis, in the other the constriction was caused by a mass of calcified tuberculous glands. Mediastinotomy with the release of the constrictive bands seems indicated in those cases of superior vena caval obstruction in which the venous pressures are increasing and in which the symptoms are progressing.

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SUSPENSION LARYNGOSCOPY IN THE TREATMENT OF MALIGNANT DISEASE OF THE HYPOPHARYNX AND LARYNX

GORDON B. NEW, M.D., F.A.C.S., and HOWARD E. DORTON, M.D., Rochester, Minnesota

DURING the eleven year period, 1927 to 1937 inclusive, a selected group of 38 patients with malignant disease of the hypopharynx and larynx have been treated at the Mayo Clinic with the aid of suspension laryngoscopy. Surgical diathermy and radium emanation seeds have been employed, and, in addition, external irradiation has been used at times.

While suspension laryngoscopy has been used for many years, its value in the treatment of malignant diseases of the hypopharynx and larynx is not generally known. We feel that carefully selected patients can be taken care of with less surgical risk when laryngeal suspension is employed. Immediate histological diagnosis by the fresh frozen section is an essential part of this method.

Lynch did more than anyone else in this country to perfect and stimulate interest in suspension laryngoscopy. In 1928, he reported dissection with a knife of early intrinsic laryngeal epithelioma under suspension and recommended its use in certain selected cases.

Killian, in giving the Semon lecture, stated that Mayer removed an epithelioma of the epiglottis in 1914 under suspension laryngoscopy but said that such cases ought to be selected with care.

At the Mayo Clinic we have used suspension laryngoscopy for many years and feel that it has a definite place in the treatment of cancer of the hypopharynx and larynx. However, the apparent lack of widespread knowledge of its usefulness is shown by a statement of Thomson in 1939 when he said, "operation *per vias naturales* is now only of historical interest, though pathologically of some importance," and he attributed the occasional rare instances of cure by this route to low grade lesions of minor extent.

SELECTION OF CASES FOR TREATMENT

Our series consisted of 38 cases of malignant disease in the hypopharynx and larynx in which treatment had been given under suspension laryngoscopy during the years 1927 to 1937 inclusive. During this same period approximately 450 patients were operated on at the clinic for malignant disease of the larynx and hypopharynx. This brings out the fact that the cases in which treatment was given under suspension laryngoscopy are a selected group.

We have divided the cases into 5 groups depending on the location of the growth: (1) growths at the base of the tongue in the hypopharynx; (2) supraglottic growths; (3) intralaryngeal growths; (4) growths involving the lateral and posterior walls of the hypopharynx; and (5) postcricoid growths. Some of these lesions involved two or more of these sites, but we grouped them according to the place where the major part of the tumor was situated. As each one of these various groups presented different problems, the selection of cases for treatment in this manner must be discussed individually rather than collectively.

Growths at the base of the tongue in the hypopharynx that were part of carcinoma of the body of the tongue were not considered; only primary growths at the base of the tongue in the hypopharynx were included. Growths in this location can be of three varieties: (1) adenocarcinoma, mixed tumor type which is usually a low grade tumor; (2) highly malignant squamous cell epithelioma of grade 3 or 4 that infiltrates into the tongue and that is an active growth, and (3) squamous cell epithelioma of low grade which does not infiltrate into the tongue but is an outgrowth from the surface of the tongue. All of these lesions are best taken care of under suspension laryngoscopy because of the difficulty of obtaining a direct view of them in a satisfactory way with any other method. Only an extensive lesion or extensive metastasis would prevent treatment in this group of cases.

The supraglottic growths consisted of those which involved the epiglottis alone or those that extend into the aryepiglottic fold, base of the tongue, or lateral wall of the pharynx (Figs. 1 and 2). Care should be taken not to attempt to treat lesions in this region under suspension

From the Section on Laryngology, Oral and Plastic Surgery, the Mayo Clinic, and the Division on Surgery, the Mayo Foundation.

Read before the meeting of the Academy of Ophthalmology and Otolaryngology, Cleveland, Ohio, October 7 to 12, 1940.

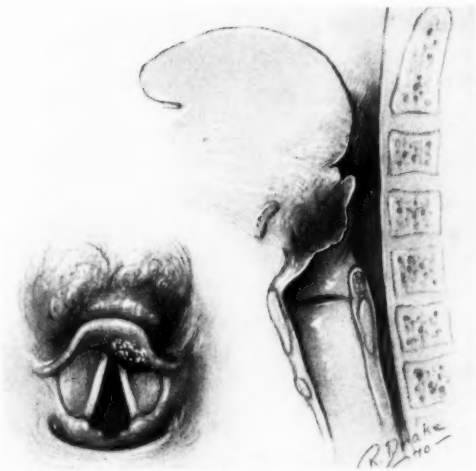

Fig. 1. In a man, aged 55 years, with squamous cell epithelioma grade 4 on the posterior surface of the epiglottis extending down into the larynx and producing edema at the base of the tongue, a preliminary tracheotomy was made, the epiglottis and growth were removed with diathermy, and emanation seeds were inserted into the base. Further radium seeds were inserted into the base of the tongue and epiglottis with no evidence of recurrence for 2 years.

laryngoscopy when lateral or subhyoid pharyngotomy, which gives much better exposure for the larger growths, is indicated. However, many lesions, particularly the highly malignant tumors, that cannot be removed by purely surgical procedures, can be treated with the aid of suspension laryngoscopy (Figs. 3 and 4).

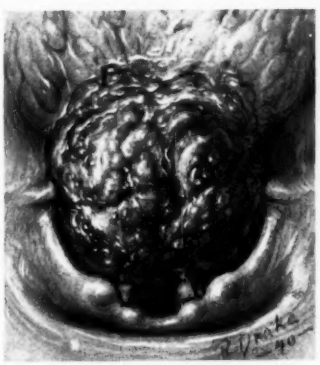

Fig. 3. In a man, aged 60 years, a squamous cell epithelioma grade 4 of the epiglottis and base of the tongue was removed after preliminary tracheotomy, July 2, 1934, and radium points were inserted into the growth. The patient has had no recurrence for six years.

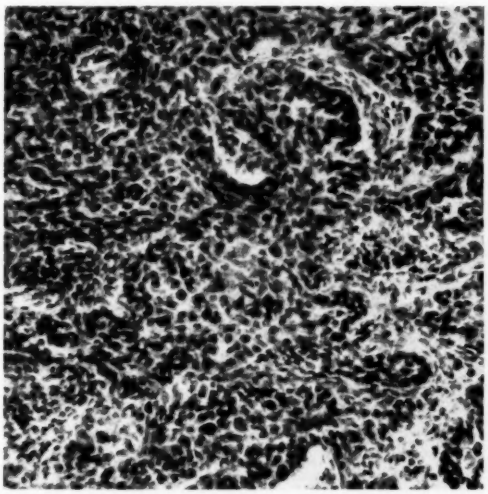

Fig. 2. Photomicrograph from same case as in Figure 1. ×180

In our series the intralaryngeal growths selected for treatment under suspension consisted of tumors of low grade or those of limited extent

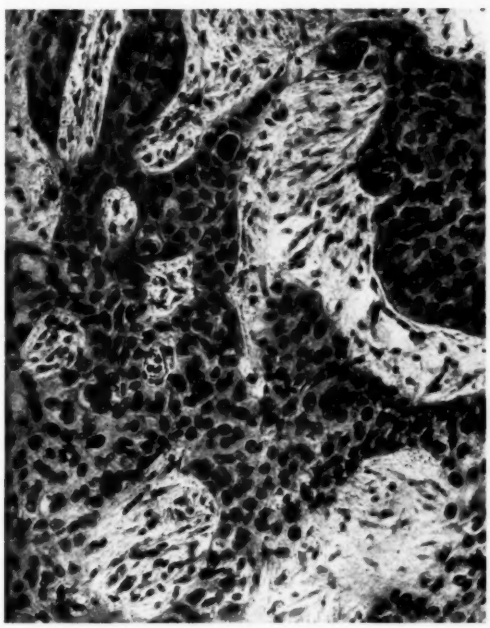

Fig. 4. Photomicrograph from same case as in Figure 3. ×180.

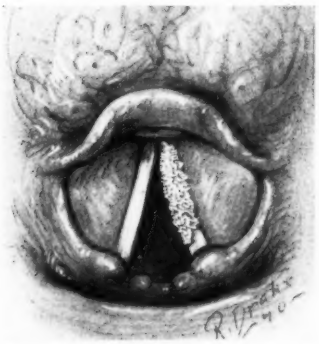

Fig. 5. In a man, aged 44 years, a squamous cell epithelioma grade 2 at the base of a leucoplacia along the anterior two-thirds of the left vocal cord was removed by means of surgical diathermy, November 20, 1936, under suspension laryngoscopy, with no recurrence for 3½ years.

on the anterior two-thirds of the vocal cord; frequently a thickened leucoplacia with early epithelioma was taken care of in this manner (Figs. 5 and 6). For elderly patients, particularly those with hypertension, diabetes, or bronchiectasis, for whom the risk from thyrotomy is increased, removal of the lesion by intralaryngeal methods is justified if the lesion is small, of low grade, and there is no fixation of the cord.

The growths, involving the lateral and posterior walls of the hypopharynx, are usually highly malignant tumors. They can be treated by the insertion of radium seeds into the lesion as well as by external irradiation. Tumors of the highly malignant type can be treated more successfully with radium than low grade tumors; consequently, small lesions of low grade should be removed with surgical diathermy.

Of the postcricoid growths only two have been treated in this series with the aid of suspension

TABLE I.—LOCATION OF LESION IN SERIES 1927–1937 INCLUSIVE

Site of Lesion	Patients		Length of life after treatment (years)	
	Total	Living last report; no recurrence	Greatest	Average
Base of tongue	10	5	5	4.7
Supraglottic region	12	8	9.5	5.8
Intralaryngeal region	11	9	4	3.6
Hypopharynx, posterior and lateral walls	3	0	7*	
Postcricoid region	2	1	7.5	
Total	38	23	9.5	4.8

*Died of recurrence.

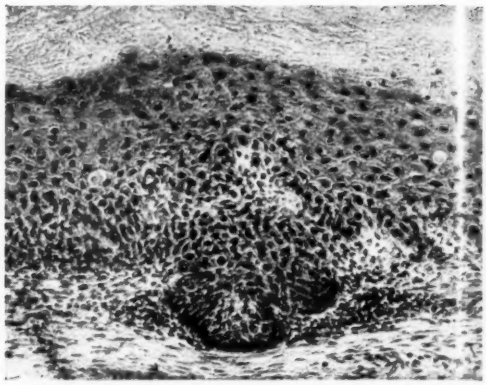

Fig. 6. Photomicrograph from same case as in Figure 5. ×128.

laryngoscopy. In most of these cases roentgen therapy with fractional doses accomplishes as much as any local treatment of the growth. It is only in the low grade lesions that we feel that external operation, by the method of Trotter in which lateral pharyngotomy is performed, gives the patient any permanent benefit.

REVIEW OF CASES

The average age of the 38 patients was 57.4 years. The youngest was a woman, aged 20 years, who had squamous cell epithelioma grade 2 of the middle third of the vocal cord, and the oldest was a man, aged 79 years, who had squamous cell epithelioma grade 4 of the base of the tongue.

TABLE II.—HISTOLOGICAL TYPE—1927–1937 SERIES

Lesion	Histological grade	Patients		Length of life after treatment (years)	
		Total	Living last report; no recurrence	Greatest	Average
Squamous cell epithelioma	1	4	3	3.8	3.3
	2	9	8	5.0	4.0
	3	9	4	9.5	7.2
	4	7	3	6.5	4.2
Mixed adenocarcinoma and squamous cell epithelioma	3	1	0	6.5*	
	4	1	0	6.5†	
Hemangio-endothelioma	1	2	1	9.5	6.2
Mixed tumor		2	1	5.0	
Lymphosarcoma		2	2	4.0	3.9
Fibrosarcoma	1	1	1	9.0	
Total		38	23	9.5	4.8

*Died of malignancy.
†Died of carcinoma of the stomach.

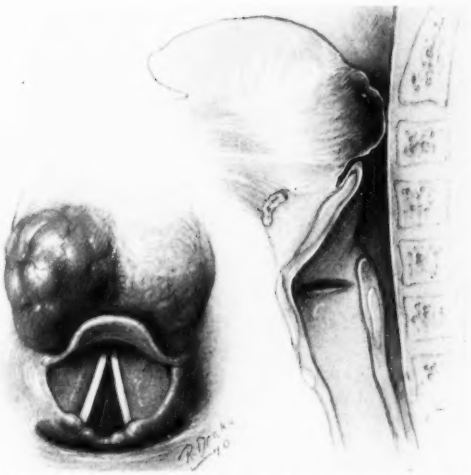

Fig. 7. In a woman, aged 70 years, a lymphosarcoma of the base of the tongue at the level of the epiglottis was partially destroyed with diathermy on June 17, 1936, and radium points were inserted into the growth. She has had no recurrence for 4 years.

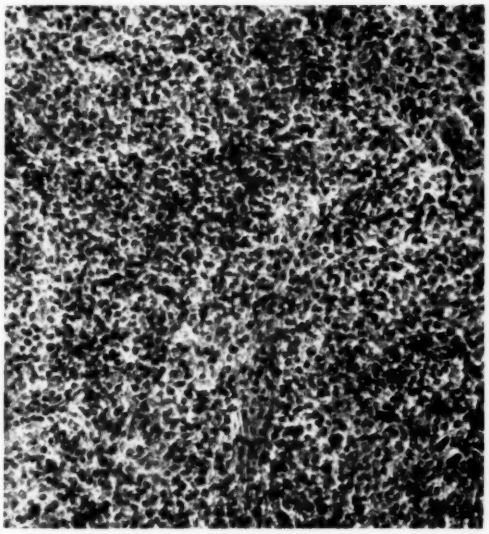

Fig. 8. Photomicrograph from same case as in Figure 7. ×190.

There were 4 women in this group; the ratio of males to females being 8.5:1. Three patients (7.9 per cent) had syphilis.

Ten lesions were situated at the base of the tongue, 12 were in the supraglottic region, 11 in the intralaryngeal region, 3 on the lateral and posterior walls of the hypopharynx, and 2 in the postcricoid region (Table I).

The most common symptoms in this group of cases were dysphagia and hoarseness. The symptoms, of course, depend on the location and extent of the lesion. Malignant lesions at the base of the tongue are frequently overlooked. The advanced lesions produce marked symptoms of pain, bleeding, and so forth, while the early lesions produce little discomfort. On this account, patients with epithelioma of the base of the tongue, epiglottis, and aryepiglottic fold usually have large lesions at the time of the first examination. Patients with early lesions of the supraglottic region frequently complain of a sensation of a foreign body in the throat while those with lesions on the vocal cords have hoarseness early and are frequently seen with a small lesion. Only 3 patients noticed enlarged glands in the neck, although 8 patients had enlarged glands in the cervical region at the time of examination.

THE METHOD OF TREATMENT

Pentobarbital sodium, 1½ grains (0.1 gm.), was administered by mouth an hour before the operation. The larynx was cocainized with a 10 per cent solution of cocaine, and the patient was then anesthetized with sodium ethyl (1-methylbutyl) thiobarbiturate (pentothal sodium) given intravenously. A 2.5 per cent solution was used. A pharyngeal tube was inserted into one of the nostrils through which oxygen was administered throughout the procedure. The pentothal sodium was administered intermittently whenever necessary.

A flat spatula attached to the suspension apparatus was employed for the lesions at the base of the tongue. For lesions of the epiglottis the spatula picked up the base of the tongue and exposed the entire epiglottis and vallecula. For intralaryngeal lesions the spatula picked up the epiglottis, and the surgeon had a direct view of the entire glottis. In all cases a specimen of the lesion was removed, a fresh frozen section was examined, and immediate diagnosis was made. Results of microscopic examination of the tissue removed are given in Table II.

In cases of carcinoma of the base of the tongue and epiglottis or aryepiglottic fold, preliminary tracheotomy was performed. After recovery the laryngeal suspension was done, and treatment was performed. For growths involving the base of the tongue (Figs. 7 and 8), radium emanation seeds were inserted into the lesion after the use of surgical diathermy. If the lesion was of limited extent, the entire treatment was completed with surgical

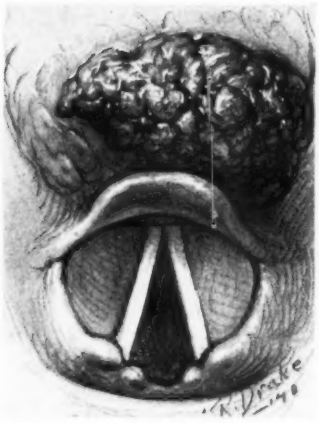

Fig. 9. In a man, aged 45 years, a squamous cell epithelioma grade 4 of the entire base of the tongue and a large metastatic mass measuring 2.5 by 2.5 by 3.5 centimeters in the cervical region was treated under suspension laryngoscopy, August 2, 1933, and radon seeds were inserted into the growth. This was followed by roentgen treatment applied externally to the neck. The patient is alive and well and without recurrence seven years after treatment.

diathermy alone. The supraglottic lesions were destroyed with a long protected diathermy point. This is a long needle covered with Duco varnish so that only the distal end of the needle is exposed. The epiglottic growths were removed piecemeal or in one piece with the Bovie surgical diathermy unit. The intralaryngeal lesions were removed with the diathermy point. No attempt was made in the primary laryngeal lesions to use radium in addition to diathermy except in unusual circumstances, for we felt that lesions extensive enough to need radium in addition to diathermy are better treated by means of thyrotomy.

In addition to treatment under suspension, radium or roentgen rays were applied to the outside of the neck, especially in cases of highly malignant growths at the base of the tongue.

TABLE III.—THREE AND FIVE YEAR SURVIVALS

Period after treatment	Patients* treated	Patients traced	Survived beyond indicated period	
			Number	Per cent
3 or more years	31	31	23	74
5 or more years	17	17	10	59

*The 3 year group comprises the patients treated 3 or more years prior to the time of inquiry, that is, 1936 or earlier; the 5 year group comprises the patients treated 5 or more years prior to the time of inquiry, that is, 1934 or earlier.

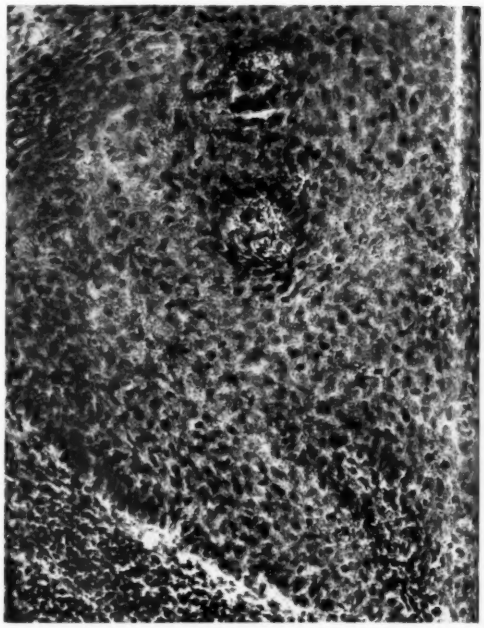

Fig. 10. Photomicrograph of specimen from the same case as in Figure 9. ×180.

RESULTS

The results of the treatment of malignant disease of the hypopharynx in the past have been very poor. The Trotter operation has produced some very striking results, but they are few. Recently fractional doses of roentgen rays as well as radium used externally have been of considerable benefit. Lenz in discussing Martin's paper reported 31 cases of hypopharyngeal malignancy; 6, 19.3 per cent, of his patients were apparently free of disease, but the length of time these patients have lived since treatment was not stated. Four of these patients had growths involving the epiglottis.

Of the 27 patients with malignant disease of the hypopharynx including the base of the tongue (Figs. 9 and 10), supraglottic region, lateral and posterior walls of the hypopharynx, and postcricoid region, we were able to trace 26, and 14, or 51.8 per cent, of the patients who were traced were alive and well.

Of the 11 patients with intralaryngeal lesions, 10 were traced and 9, or 90 per cent, were alive and without recurrence. These patients had small, low grade lesions which account for this very high percentage of cures.

Nine of the traced patients, or 25 per cent, died of cancer, the majority within a year and a half of the final treatment. One of the group now dead lived 7 years, and another of the group, 6½ years.

There was 1 postoperative death; the patient died of bronchopneumonia 8 days following treatment of an epithelioma at the base of the tongue. The patient did not have a preliminary tracheotomy.

The 3 and 5 year survivals are shown in Table III. Of 31 patients treated and traced for 3 or more years (operations were performed in 1936 or before), 23, or 74 per cent, lived more than 3 years. Of 17 patients treated and traced for 5 years (operations were performed in 1934 or earlier), 10, or 59 per cent, lived more than 5 years. In the series there were 3 patients who have lived more than 9 years following treatment, and all of these are living at the time of this report (1940).

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THE DEMONSTRATION OF MYCOBACTERIUM TUBERCULOSIS IN ANORECTAL ABSCESS

JOSEPH E. POTTENGER, M.D., and F. M. POTTENGER, Jr., M.D.
Monrovia, California

An abundant literature is available reporting various diagnostic laboratory procedures for the demonstration of Mycobacterium tuberculosis in fistula in ano. Recently Buie, Smith, and Jackman reviewed the subject calling attention to the almost universal failure to demonstrate the organism by direct staining methods. They recommended guinea-pig inoculation. Quite recently Joynt confirmed the general conclusions of previous writers and employed culture methods in place of the guinea-pig. In relation to the antecedent condition, anorectal abscess, demonstration of the organism by direct microscopical methods has not been reported with any important degree of success. In institutions where patients are continuously under observation we may anticipate the spontaneous rupture of these abscesses by aspirating the contents. During the past 9 years we have successfully aspirated 16 of a total of 20 abscesses under observation.

CLINICAL MATERIAL

This report is concerned with the investigation of 22 abscesses from 19 patients. All patients furnishing material for examination had positive sputum except 1 whose pulmonary history was unknown, as the specimen was sent in by an outside physician. One patient had 3 distinct abscesses form over a period of 1 year. Another had 2 abscesses during a 4 months' period.

Sixteen abscesses were successfully aspirated. Rupture during preparation for aspiration occurred 4 times and spontaneous rupture occurred from 1 week to 4 months before investigation in 2 instances.

PROCEDURE

The syringe and needle No. 16 were sterilized at 220 degrees C. dry heat for 1 hour. The investigation of the material was made with the dilution-flotation procedure (3), and guinea-pig inoculation. All animals were tested before they were used with 0.1 cubic centimeter purified protein derivative second strength. The same dose was given as a diagnostic test on the twentieth day after inoculation.

From The Pottenger Sanatorium, Monrovia, California.

The pus diluted 10 times with 0.5 per cent sodium hydroxide was shaken in a strong shaker for 5 minutes and set at 37 degrees for 1 hour, or in case contaminating organisms were present, for 2 hours. Thorough homogenization was accomplished by 10 minutes shaking. The centrifuge was employed at 1000 revolutions per minute for 2 minutes, to throw down undigested tissue fragments. The upper third of the solution was pipetted off, placed at 55 degrees C. for 30 minutes to complete the digestion process and used for dilution-flotation. The final dilution with distilled water was made so that the amount of the original material contained in the fraction would be diluted 100 times. (On account of the high protein content of this type of material it is necessary to dilute to a much greater degree than is necessary in the case of sputum.) From 0.5 to 1 cubic centimeter of xylol was added, and the mixture shaken for 10 minutes. Films were made from the xylol layer by means of a capillary pipette. The exact number of organisms found in a 10 minute search was recorded if present to the extent of one in two fields or less.

For guinea-pig inoculation the remaining two-thirds of the digested specimen was employed. It was neutralized with 3 per cent hydrochloric acid in the presence of brom-thymol-blue, and injected subcutaneously in divided dosage in 2 or more regions. (If all the inoculum is given in one region, pyogenic ulceration may occur early and expel the organisms before infection takes place. Ulceration of all inoculation sites in case of divided dosage is a rare event.) We had but 1 early pyogenic abscess in the series. The animal, however, was positive. In 9 animals the inoculation was made intraperitoneally. Not a single animal was lost by death due to other causes.

RESULTS OF INVESTIGATION

Of 20 abscesses and 2 recently formed sinuses investigated 4 showed from 2 to 10 organisms per field, so that confirmation by inoculation was not needed. The results obtained by dilution-flotation and guinea-pig inoculation of material obtained from the remaining 18 abscesses are tabulated in Table I. The table presents 3 groups of

TABLE I.—FINDINGS BY DILUTION-FLOTATION AND GUINEA-PIG INOCULATION IN 18 ANORECTAL ABSCESSES AND RECENTLY FORMED FISTULAS IN 14 KNOWN TUBERCULOSIS PATIENTS

Specimens	No. of examinations	Average amount c.cm.	D.F.+ G.P.+	D.F.− G.P.−	D.F.− G.P.+	D.F.+ G.P.−
Aspirated	13	2.66	12	1	0	0
Ruptured at operation	4	0.49	2	1	1	0
Ruptured 4 mos. before investigation	1	0.01	0	0	1	0
Totals	18		14	2	2	0

D.F., dilution-flotation.
G.P., guinea-pig.

results. The first consists of 13 successfully aspirated abscesses averaging 2.66 cubic centimeters. The second consists of 4 abscesses which ruptured into the anal canal under pressure from the speculum resulting in much loss of material and averaging 0.49 cubic centimeter of material recovered. The third group represents a single specimen in which a very small amount of serous discharge was obtained from a fistulous tract which had formed 4 months previously.

In the first group of successful aspirations dilution-flotation and guinea-pig inoculation were in 100 per cent agreement, 12 positive and 1 negative result. In the second group of 4 abscesses rupturing under pressure, agreement resulted in 3 instances, 2 positive and 1 negative; and in the fourth instance in which only 0.05 cubic centimeter of material was obtained, dilution-flotation was negative but the guinea-pig was positive. In the third group dilution-flotation was negative and the guinea-pig was positive.

The total of the 3 groups shows 18 specimens in which dilution-flotation and inoculation were in agreement 16 times. Fourteen specimens were positive and 2 negative. It should be noted that the 2 failures by dilution-flotation occurred with materials small in amount, following spontaneous rupture.

TABLE II.—RANGE OF THE NUMBER OF ORGANISMS FOUND IN 18 SPECIMENS POSITIVE BY DILUTION-FLOTATION

	Times Found
1 in 2 fields to 10 per field	8
Organisms found in 10 minute search	
15 to 79	1
1 to 14	9

Elsewhere (3, 4) the relative sensitivity of homogenized smears counterstained with strong methylene blue, with picric acid, and the same material treated by dilution-flotation counterstained with picric acid is given as 1, 5.5, and 80, respectively. Applying these ratios to Table II, 8 of the 18 specimens, or 44.4 per cent should be positive by Ziehl-Neelsen with methylene blue counterstain. If picric acid is used, another specimen should be positive, making 9 positives in a total of 18 or 50 per cent. Nine specimens should be found positive only by dilution-flotation. This is the group in which the organisms are so rare that they may be found by Ziehl-Neelsen only by prolonged search of an hour or more. Even with the 15-fold enrichment attained by dilution-flotation only 4 organisms were found in 1 specimen in 1 hour's search. In the remaining specimens the organisms were found during the first 5 minutes' search. Ziehl-Neelsen counterstained with picric acid was carried out in 7 of the 18 specimens, 4 of which, or 57.1 per cent, were positive. This percentage agrees well with the probable percentage deduced from the known sensitivity ratios.

The actual number of organisms found in the 9 specimens per cubic centimeter of material is small. Corper established about 100,000 organisms per cubic centimeter as the lower limit of sensitivity of the Ziehl-Neelsen method and since dilution-flotation with picric acid counterstain is 80 times more sensitive, a single bacillus found in 10 minutes' search would indicate $100{,}000 \div 80 = 1250$ organisms per cubic centimeter. The number of organisms, 1 to 14, found in a 10 minute search would indicate the presence of 1250 to 17,500 organisms per cubic centimeter of original material investigated.

EVALUATION OF STUDY

In view of the unprecedented success with which we have demonstrated Mycobacterium tuberculosis in this series of abscesses, we wish to point out the causes of failure of earlier workers. First, the selection of the optimum time for aspiration has not been duly considered. It is well established that the number of organisms in tuberculous lesions increase greatly at the time of caseation and liquefaction. Following removal of the abscess contents by spontaneous rupture, the organisms decrease rapidly so that their demonstration is difficult. Second, an adequate enrichment and a light counterstain is absolutely necessary for maximum results.

Undoubtedly many, perhaps most, of these abscesses rupture spontaneously before the surgeon is consulted, thus the best conditions for direct and immediate investigation have disappeared.

It is evident that a method that can give a definite diagnosis within 2 hours after the specimen is received by the laboratory offers a distinct advance over former practice. In 1 of these cases a negative result by dilution-flotation led us to refrain from surgical procedure. The abscess healed spontaneously and 2 months later the guinea-pig confirmed the negative findings.

SUMMARY AND CONCLUSION

A comparison of the results obtained by dilution-flotation and guinea-pig inoculation in the demonstration of Mycobacterium tuberculosis in 18 anorectal abscesses is presented.

The two methods were in 100 per cent agreement in 13 abscesses aspirated by needle. Twelve were positive and 1 was negative by both. Under less favorable conditions in which the abscesses ruptured spontaneously with much loss of material, they were in agreement in result in 3 of 5 abscesses investigated. Two were positive and 1 was negative by both. In the 2 other abscesses dilution-flotation was negative and inoculation was positive.

Dilution-flotation with picric acid counterstain offers a means for the immediate diagnosis of anorectal tuberculosis in the abscess stage, or its probable exclusion.

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EDITORIALS

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MAY, 1941

THE SURGICAL NURSE

THE development of surgery is still in a relatively youthful stage. Its emergence from the era when its scope was greatly limited by lack of knowledge concerning antisepsis and asepsis and by the fact that anesthesia had as yet not been developed is still within the memory of many and even the personal experience of a few. Since the advent particularly of these two so desirable adjuncts, surgery has been busily occupied and satisfactorily pleased with itself—because with these aids so many more things can be accomplished than previously. This later era was characterized by exploration, discovery, and development and to those devoting their lives to surgery, has been most gratifying and satisfactory. So rapid has been the development, however, that of necessity its rate of speed must and has slowed down. As is true of any rapid advance, this is probably a very good thing since time and opportunity are afforded to review, refine, and consolidate the gains made and thus improve the quality of surgery.

A great deal of attention has been given to surgical technique, surgical instruments, appliances, anesthetic agents, anesthetic apparatus, and the anesthetist, and great progress has been made regarding these phases of surgery during the past few years. Surgical assistantships, a form of surgical apprenticeship, have always been a part of surgery, and much progress has been made in this branch of training for surgery. This may not be said of the training of the surgical nurse, however. A very essential part of any operating surgical group is the table or operating nurse, and it is regarding the methods of training this group that I wish to direct attention.

In early days, the surgeon assumed the responsibility for all details of the operative procedure, even to the administration of the anesthetic. Today, however, surgical procedures have become so complex that the entire thought and concentration of the operating surgeon are required. Hence it is now necessary that each member of the operating team be well trained, competent, and alert. This is especially true of the surgical nurse who can do so much to relieve the surgeon by taking care of many of the necessary details involved in the carrying out of any operation.

Why those responsible for the training of nurses should assume that as a part of her training every nurse should be required to assume responsibility at the operating table has always been difficult for me to understand. One nurse in a hundred will become a surgical nurse and not more than one in twenty or thirty will show even a moderate aptitude for

that particular branch of nursing. A nurse not possessed of such an aptitude and yet required to serve as a surgical nurse will suffer mentally because of her lack of experience and her ineptitude; in fact, she will be more of a hindrance than a help to the surgeon and indeed, in some immeasurable degree, may be responsible for increased morbidity or mortality percentages.

It is an accepted fact that a surgical operation is a serious undertaking and therefore anyone taking part in such an undertaking must be capable, well trained, and experienced. If it is required that those who desire to become surgeons take special training to demonstrate their fitness to do surgery, then similar standards of training and requirements should be established for the training of that very important part of the surgical team—the surgical nurse. Just as the prospective surgeon must take postgraduate training in surgery, so should the nurse wishing to qualify as a surgical nurse be compelled to take postgraduate training in operating room technique. When, as part of their training, undergraduate nurses are assigned to the operating room, they should be under the supervision of trained and experienced operating table nurses and should work only as second nurses. In such a position they will not handicap the operating surgeon; they will be more calm and hence, be better able to learn under the direction of one with sufficient experience and knowledge to teach them. Unfortunately it is true that the less experienced the surgeon the more apt he is to have to work with a relatively inexperienced and inept surgical nurse, despite the fact that he should be relieved of any confusion or lack of co-operation and should be free to concentrate exclusively on the operative procedure.

The time is not far distant when both that surgeon and that hospital will be out of step with the times who do not include in operating teams an anesthetist who is qualified to employ all of the newer developments in the administration of anesthetics, an assistant who is at least in the process of being trained to carry out all of the major surgical procedures, and an operating nurse who has been specially trained for a relatively permanent position.

FRANK H. LAHEY.

AN EVALUATION OF THE METHODS OF TREATMENT OF CRYPTORCHIDISM

THERE is a diversity of opinion among surgeons as to the best treatment for the undescended testis. Some believe that the ectopic gland is potentially malignant and should be removed. It should be said, however, that the undescended testis should not be considered a precancerous lesion as only about 2 per cent of such organs develop tumors (Hinman). Others believe that if left alone, most of these retained gonads will descend spontaneously. The reports of some investigators have indicated that the results from hormonal therapy are equally as good as, if not superior, to those obtained by surgical treatment (orchiopexy). In formulating a rational plan of treatment of the undescended testis, one is influenced by the number and type of cases he has seen, his surgical experience and that of his associates, and the type of case that receives hormonal therapy.

It is an important question: What percentage of undescended testes descends spontaneously? If the majority of ectopic testes will eventually descend of their own accord as some investigators claim, the value of any kind of therapy is questionable.

There can be no doubt but that some aberrantly placed testes migrate to the scro-

tum of their own accord (Drake, Williams, Johnson). There is a difference in the reported incidence of ectopy before and after puberty. According to Johnson, Williams and Drake, the incidence of cryptorchidism in younger boys is 1.7 to 4.2 per cent; in adult men gonadal ectopy occurs in 0.2 to 0.3 per cent. This may mean that the hormonal changes incident to puberty produce descent in a large percentage of cases. However, another explanation may be the inclusion in the prepubertal group of a number of testes of the migratory or retractile type (physiological ectopy, pseudocryptorchidism, or ectopy *en retour*). It is important to differentiate true (anatomical) from the pseudo or physiological type of cryptorchidism, as many cases of the latter descend spontaneously into the scrotum at puberty. There is no convincing evidence that testes anatomically retained by mechanical obstructions to descent ever descend spontaneously. Moreover, the finding of cryptorchidism in adult men is irrefutable evidence that all undescended testes do not descend spontaneously.

The treatment of undescended testes by gonadotropic substances is generally recognized, but the results of treatment are varied. Bigler, Hardy, and Scott and Nixon in their reviews of the early literature found that descent was said to occur in 60 to 75 per cent of cryptorchids treated with pituitary or pituitary-like extracts. Later reports have been less enthusiastic. The studies of Thompson and Heckel, Mimpriss, and Rea showed descent in only 16 to 31 per cent of ectopic testes treated by endocrine therapy. The dosage and length of treatment with anterior pituitary-like substances is quite varied in the cases reported in the literature. Thompson and Heckel wonder if the percentage of patients showing descent spontaneously at puberty would be the same as that following the use of anterior pituitary principle before puberty. Thus, as a result of hormonal therapy, descent of the testis would be obtained only in those cases in which the testes would descend normally at puberty.

It is impossible to give a final estimate of the value of gonadotropic substance in the treatment of ectopic testes. For one thing, the incidence of spontaneous descent is not accurately known. Furthermore, it must be ascertained whether endocrine therapy causes descent only of those testes which would descend without therapy about the time of puberty. Hormonal therapy may make it possible to differentiate between those testes which require surgical interference because of mechanical obstruction to descent and those that do not.

Treatment of the retained testis may be deferred until the patient is nine to eleven years old, since the testis does not grow grossly or microscopically until puberty, (Wangensteen). If one cannot be certain that the case is one of pseudocryptorchidism or true undescended testis, there is no great harm in waiting until after puberty before instituting treatment. The practice of delaying treatment too long is to be condemned, however, knowing how atrophic the testis becomes when left in an aberrant position.

A course of hormonal therapy should be given first to see if the additional hormonal stimulus will cause the gonad to descend into the scrotum. If no results are obtained, an orchiopexy should be performed. From the experience at the University of Minnesota Hospitals, it may be said that (a) spontaneous descent of a true undescended testis is a rare occurrence, (b) that the results following the use of gonadotropic substance in cryptorchidism have been disappointing, and (c) that the most satisfactory treatment of extopic testis is orchiopexy.

CHARLES E. REA.

Christian Fellow

TEXTS AND DOCUMENTS

TO A MEDICAL GRADUATE UPON BEGINNING HIS HOSPITAL INTERNESHIP

IN the main corridor of the Cook County Hospital beside the elevators that carry a never ceasing stream of doctors, internes, nurses, visitors, is a bronze plaque inscribed in memory of Christian Fenger. The interested reader cannot but wonder, "What sort of man was this to merit such recognition?" and the thoughtful interne may ask himself, "Could I accomplish anything to merit such a tribute from my successors?"

The story of Christian Fenger, of his life and of his contributions to surgery, and particularly to Chicago surgery, has been told many times[1]—only recently in a beautiful tribute by Dr. James B. Herrick.[2] Everyone has dwelt particularly on his prolonged preparation for the practice of medicine, his indefatigable industry, his willingness to help young men. In Billings' words:

". . . soon after his arrival in the country, he was persuaded by his countryman and friend, Dr. S. J. Jacobson, to locate in Chicago. Dr. Jacobson introduced Fenger to the members of the staff of the Cook County Hospital and he was invited to conduct a few autopsies at that institution. His scientific demonstration of pathological anatomy created such an impression that Dr. Isaac N. Danforth, who held the appointment of pathologist to Cook County Hospital, immediately tendered his resignation for the purpose of making the position available to Fenger. From the spring of 1878 until 1893, Fenger was the chief pathologist at the County Hospital; for 14 or 15 years the autopsy room at the County Hospital was the Mecca of medical students, internes, and members of the medical profession of Chicago who for the first time in the medical history of the Middle West had an opportunity to witness scientifically conducted autopsies and to learn the fundamentals of morbid anatomy and pathology.

"In 1879, Fenger served in the surgical wards for the various members of the surgical staff of the hospital when they were absent from the city on vacations. This surgical service gave him the opportunity to introduce Listerism—antiseptic surgery—in the Middle West. In 1880 Fenger secured appointment with a regular surgical service in the County Hospital in which he continued for the next 12 years.

"From 1880 to 1884 he was curator of Rush Medical College Museum; in 1884 he was appointed professor of surgery in the College of Physicians and Surgeons; in 1893 he became professor of surgery in the Northwestern University Medical School, and in 1899 he became professor of surgery in Rush Medical College affiliated with the University of Chicago. He was surgeon in chief of the Passavant Memorial Hospital, the German Hospital of Chicago, and the Lutheran Tabitha Hospital from the time they were organized until his death. From 1893 to 1899 he was attending surgeon at the Mercy Hospital, Chicago, and from 1899 until his death, he was attending surgeon at the Presbyterian Hospital. . . .

". . . he won success in practically every project undertaken. His knowledge of morbid anatomy and of pathology was phenomenal for that day and was attained by unremitting energy during his life in Denmark and Egypt and his earlier experience in the United States. This knowledge of pathology and of morbid anatomy made him one of the great surgeons of his time. He never became a brilliant operator, but what he lacked in operating skill was more than compensated for by thoroughness and knowledge of pathology. In diagnosis he was unsurpassed by any of his living contemporaries. He spoke five or more modern languages, but did not possess a ready command of any language. Nevertheless, he was a great teacher and though his speech was usually marked by halting words, he was able to impart knowledge to others with greater clearness than most teachers with fluent speech. He was especially fond of young men who showed by their every day lives that they had a thirst for knowledge and expressed this by purposeful, enduring work. He spent hours of his valuable time, both of the day and night, in the instruction of young medical

[1] Frank Billings. Surg., Gynec. & Obst., 1922, 35: 365–369. Alton Ochsner. South. M. J., April. 1938, 447–451.

[2] Proceedings of the Institute of Medicine of Chicago, 1941, 13: 318–329.

men; in these interesting conferences he frequently forgot the passage of time in the apparent joy of teaching. It was through his influence that many of the young medical men of the period from 1880 to 1900 visited the clinics of Germany, Austria, France, and England, and later became leaders in their chosen fields of work in the United States. While Fenger loved above every other thing in his professional life to help young men who were not afraid to work, he expressed an impatience with the frivolous and indolent men with whom he came in contact. Always he had the courage of his convictions and expressed them with blunt words which sometimes gave those unacquainted with him the idea of unfriendliness. But no man the writer has ever known was freer of envy or jealousy of others. Always he availed himself of every opportunity to express appreciation of the work of other men, provided it was characterized by honesty and efficiency. He was honest, intellectually and professionally. He was sincere and by nature simple in his deportment and daily life. He was free from cupidity and sympathetic with the poor; to each patient he applied all of the knowledge he possessed and all of the time necessary disregardful of financial reward.

"Fenger lived in Chicago 24 years. During that period of time he exerted an influence in scientific medicine unequalled by any other individual. It was due to his influence and particularly as a pathologist that there developed such men as Nicholas Senn, John B. Murphy, William J. Mayo, Lewis L. McArthur, and many others celebrated as great surgeons, and Ludvig Hektoen, E. R. LeCount, H. G. Wells, and others recognized as great pathologists, and many practitioners of internal medicine throughout the Middle West and in Chicago. . . .

". . . Christian Fenger passed from this life on March 7, 1902, but though 20 years have passed, he lives today in the hearts and minds of hundreds of physicians and surgeons who were proud to call him master; and he will continue to live through other generations by the work of his students and his pupils' students."

The rewards that came to Fenger were those that every doctor comes to prize above all others —the esteem, the affection, and the wholehearted admiration of his fellow practitioners.

Not long ago in a publication emanating from an interne group there appeared "Our Platform," and among other "planks" the following:

"Expansion of the educational program.

"Preferential consideration for our internes in making appointments for residencies.

"Financial remuneration for internes."

The contrast with the spirit and principles of action that motivated Christian Fenger's life struck me so forcibly that I was impelled to draw up a "platform" which seemed to me consistent with the spirit of a great institution. Perhaps I should call it "Resolutions Made on Beginning an Interneship:"

To be grateful for unlimited opportunity to expand my medical horizon in a relatively brief period of time and in unusually favorable surroundings. To appreciate the privilege and opportunity of following in the steps of Christian Fenger and Nicholas Senn; or perhaps of Maurice Richardson, of Homans and Cabot; or of Halsted and Osler and Finney. To emulate their example and to prove a worthy successor to them.

To co-operate with everyone on my service so as to render the most efficient possible care to the patients entrusted to me. As a junior to be loyal, prompt, ready for any task that will help to "make things go." As a senior to direct and organize the work of the ward so that the younger men will secure the maximum of training and experience; so that the medical students who come to the hospital as clerks will strive to secure a place on our service; so that the nurses will feel it is an opportunity and privilege to help care for our patients.

To treat with special consideration the patients who come under my care, knowing that many of them are the world's less fortunate children and that they are in the hospital, not because of their confidence in my ability to help them, but because they have nowhere else to go.

To be sympathetic and kindly to relatives and friends, realizing that in the practice of medicine one must consider the family as well as the patient, and that unless I can gain and hold the confidence of both my efforts may be fruitless. To remember that the reaction of the responsible member of the family to a request for consent to postmortem examination of the baffling and unusual case that has not responded to treatment may depend entirely on the impression he has gained as to the degree and sincerity of my interest in the patients under my care.

To make an accurate record of the history and of the examination of each patient so

that the evidence may be complete and permanent. To keep notes of important cases with names, dates, and diagnosis, so that I can recall them for reference when the occasion arises.

To leave no stone unturned to make an exact and accurate diagnosis of every patient in my ward.

To give every patient under my care the benefit of the best treatment that the hospital and modern medical science afford.

To make a list each morning of the half dozen patients that require special care and attention for the next 24 hours if they are to recover from the serious illness they have contracted. To explain the need for special care to the responsible nurses, so that their interest is quickened and their efforts directed with intelligence and effectiveness.

To try to anticipate trouble and not to wait until catastrophe stares us in the face. To provide a suitable donor and to be ready for blood transfusion before the patient is *in extremis*, to give the intravenous fluid before dehydration is obvious to the most casual observer. To prepare my surgical cases properly for operation; to see that the necessary instruments and apparatus are available and in good order, to provide for the cast or splint or retention apparatus that may be needed after operation.

To ask myself each evening before I leave the ward if there is something still undone that cannot wait until morning—some case of bleeding to check for evidence of recurrence, some splinted arm or leg to check for position or pressure of bandage or cast, some intravenous fluid to be given.

To keep on my bedside table some journals and books, so that every evening before I turn off my light I can spend 20 minutes reading the *Journal of the American Medical Association*, SURGERY, GYNECOLOGY AND OBSTETRICS, the *Annals of Surgery;* or the life of Christian Fenger, of Robert Jones, of Osler—men after whom I would wish to pattern my life and conduct.

To remember that if I "do today's work today" I need not be concerned about tomorrow and next month and next year.

"... in the summer of 1871, when I was attending the Montreal General Hospital, much worried as to the future, partly about the final examination, partly as to what I should do afterwards, I picked up a volume of Carlyle, and on the page I opened there was the familiar sentence—'Our main business is not to see what lies dimly at a distance, but to do what lies clearly at hand.' A commonplace sentiment enough, but it hit and struck and helped, and was the starting-point of a habit that has enabled me to utilize to the full the single talent entrusted to me. . . .

"The load of to-morrow, added to that of yesterday, carried to-day makes the strongest falter. Shut off the future as tightly as the past. No dreams, no visions, no delicious fantasies, no castles in the air, with which, as the old song so truly says, 'hearts are broken, heads are turned.' To youth, we are told, belongs the future, but the wretched to-morrow that so plagues some of us has no certainty, except through to-day. . . . The day of a man's salvation is now—the life of the present, of to-day, lived earnestly, intently, without a forward-looking thought, is the only insurance for the future. Let the limit of your horizon be a twenty-four hour circle. On the title page of one of the great books of science, the *Discours de la Méthode of Descartes* (1637), is a vignette showing a man digging in a garden with his face towards the earth, on which rays of light are streaming from the heavens; above him is the legend 'Fac et Spera.' 'Tis a good attitude and a good motto. Look heavenward, if you wish, but never to the horizon—that way danger lies. Truth is not there, happiness is not there, certainty is not there, but the falsehoods, the frauds, the quackeries, the *ignes fatui* which have deceived each generation—all beckon from the horizon, and lure the men not content to look for the truth and happiness that tumble out at their feet. Once while at College climb a mountain-top, and get a general outlook of the land, and make it the occasion perhaps of that careful examination of yourself, that inquisition which Descartes urges every man to hold once in a lifetime—not oftener.

"Waste of energy, mental distress, nervous worries dog the steps of a man who is anxious about the future. Shut close, then, the great fore and aft bulkheads, and prepare to cultivate the habit of a life of Day-Tight Compartments. Do not be discouraged—like every other habit, the acquisition takes time, and the way is one you must find for yourselves. I can only give general directions and encouragement, in the hope that while the green years are on your heads, you may have the courage to persist." ("A Way of Life" by William Osler. An Address delivered to Yale Students.)

It has often been said, "The world bows down to the man who works." It might be said with equal truth that the world is likely to pass with impatience, and perhaps a touch of scorn the man

who constantly stands with outstretched hand and plaintive voice saying, "Gimme."

A beautiful tribute to Sir Robert Jones in the *Journal of Bone and Joint Surgery*, in 1933, vol. 15, pp. 541–543 begins and ends with the following paragraphs:

"The kindly word, the cheering smile, the twinkling eye, the whole magnetic personality of Sir Robert Jones remains only as a memory. The world's greatest orthopaedic surgeon has completed his life's work; quietly as he was born seventy-four years ago at Rhyl on the North Wales coast, just as quietly he died in the early days of this year at a little village in Montgomeryshire. . . .

"Throughout his career he practised in Liverpool, and Liverpool has paid its last and greatest tribute to the honor of one of its citizens. The ashes of Sir Robert Jones are the first to find a resting place within the walls of the Cathedral. The urn stands on a column of stone, close to the foundation pillar, beneath the stained glass window dedicated to 'Service.' As long as the walls of that vast cathedral stand, they will shelter all that has died of Robert Jones, as a token and a memorial of his service to mankind. In the hearts and minds of those who came within the glow of his presence and who learned humbly to love him, his spirit still lives."

It was the spirit of Service that inspired and motivated the lives of Fenger and Osler and Robert Jones; and it is that spirit that will bring life's finest rewards to their successors who are just beginning their careers in the profession in which we are proud to be enrolled.

SUMNER L. KOCH.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

A TREATISE on genito-urinary diseases is presented by Pelouze in *Office Urology*.[1] He emphasizes the medical aspects of a urologic office practice. The anatomy and physiology of the genito-urinary tract are briefly given as a background for the analysis of the disturbed physiology and pathological lesions.

In this volume a most competent, experienced authority exposes to the reader the secrets and difficulties encountered in a successful urologic practice. Necessities, such as adequate office floor space, cleanliness, and equipment for simple routine laboratory procedure are covered in detail.

The discussion of gonorrhea is priceless. In simple and plain language the diagnosis and the gentle art and science of its treatment are uniquely presented. Adequate reasons for routine office use of Gram's stains are given. The pitfalls in smear diagnosis are likewise emphasized. Gram positive cocci may be mixed with gram negative ones due to variation in size, dye intensities, mutation or fission forms. Uncertainties of identification of cocci by cultures are pointed out. Subculture from liquid medium to solid medium will invariably change the chain formation on smears to clusters. The author states he has reached a point "where he does not know a staphylococcus from a streptococcus in ordinary cultures." In the treatment of gonorrhea the value and shortcomings of sulfanilamide and its derivatives are brought up to date. The fact that many patients remain carriers following sulfanilamide therapy is forcibly brought to the reader's attention. A warning to include a culture for the gonococcus in the criteria of cure in all patients treated with sulfanilamide is added to spare many innocent victims the disease.

The recognition and management of specific and nonspecific prostatitis is most comprehensive. The physician must be thoroughly familiar with the normal to recognize and interpret the abnormal. Not all normal secretions come from normal prostate glands. Repeated examinations will show evidence of infection and not irritation of a normal gland. Seminal vesiculitis is deflated as a common focus or harborer of infection. Seminal vesiculograms are rarely indicated.

Adequate drainage is given as the primary remedial measure affecting genito-urinary infections. The following points are neatly made: (1) All genito-urinary infections produce pus. (2) In the presence of pus good drainage is essential. (3) All things equal—the better the drainage, the better is the response. (4) Chronicity is the result of poor drainage. (5) An organ has an inherent tendency to get well unless there is an effective feeder in some poorly draining contiguous organ.

The influence of the mind upon the urinary and sexual function is well presented. Frequency of urination and nocturia may be psychic in origin. Urinary retention may be functional. To search the mind as well as the urinary tract is a safe precaution. Psychogenic sensory symptoms are not imaginary any more than the pain of a true neuritis.

A comprehensive review of this textbook reveals a brief inclusion of all major urologic lesions, diagnostic procedures and treatment, medical, instrumental, and operative. One is strongly impressed with the inseparability of "office urology" and "hospital urology." This volume should prove most helpful and instructive to all who are interested in genito-urinary infections. LEANDER W. RIBA.

THE concise and well written volume of 135 pages by Handfield-Jones entitled *Surgery of the Hand*[2] is an excellent contribution to the subject of hand surgery and emphasizes again how far-reaching and important have been the results of Kanavel's pioneer work on infections and injuries of the hand. In his preface the author acknowledges his indebtedness to Kanavel, and in discussing the subject of infection and injury constantly refers to his teachings. Two-thirds of the volume is devoted to a discussion of infections of the hand and their sequelae, a second section of 23 pages to injuries, and the final section of 21 pages to other surgical lesions.

In reviewing a volume which is so well written and which stresses wisely and forcefully correct surgical principles it may seem unduly critical to select anything for adverse comment and in doing so we would not detract from the commendation that has been expressed. In discussing prevention of infections after injury the author states (p. 7) "Should the hand be dirty . . . more harm than good can be done by washing. The injured part is immersed in a bath of tincture of iodine for three minutes, the skin edges being separated to give access to the iodine." One would like to substitute for this advice the suggestion that simple soap and water cleansing followed by irrigation with sterile salt solution, if carried out within 2 hours of the time of injury, is an ideal method of transforming a contaminated wound into a clean surgical wound that can be re-

[1] OFFICE UROLOGY; WITH A SECTION ON CYSTOSCOPY. By P. S. Pelouze, M.D. Philadelphia and London: W. B. Saunders Co., 1940.

[2] SURGERY OF THE HAND. By R. M. Handfield-Jones, M.C., M.S., F.R.C.S. Baltimore: The Williams & Wilkins Co., 1940.

paired and closed with safety and with every likelihood of primary healing.

On page 100 the author states, "I believe that immediate suture of an ensheathed tendon is both futile and dangerous whereas a free tendon should be united at once." Such advice seems to ignore the fact that the result of any tendon suture depends first of all upon securing primary wound healing and without infection. *No* tendons should be sutured unless the surgeon is convinced that the wound is a clean surgical wound. The fact that infection is likely to be more disastrous if it occurs within a tendon sheath does not affect the essential principle involved.

Throughout the volume excellent illustrations have been used which add greatly to its attractive appearance and to clarity of the discussion. Altogether, this contribution is an excellent and desirable addition to the literature of surgery of the hand.

SUMNER L. KOCH.

THE two volume set entitled *Abdominal Operations* by Maingot,[1] containing some 1300 pages, would seem to be more properly entitled "Surgical Conditions of the Abdomen" since at least as much space is devoted to discussion of the etiology, pathology, symptoms, and diagnosis as is given to the operations. There are many nicely executed drawings of operative procedures which help clarify the accompanying descriptions.

The first volume covers abdominal incisions, stomach and duodenum, spleen, pancreas, gall bladder and bile ducts. These subjects are fully discussed and many references are made to the current literature, though not always to the most recent contributions. A more critical stand by the author in handling the subject of suture materials and wound closure technique would be thought desirable by many surgeons. The operations of the stomach and duodenum are covered in considerable detail.

Volume 2 considers the liver, appendix, peritoneum, mesentery, omentum, external abdominal hernia, intestines, and postoperative chest conditions. The greatest allotment of space is given to the vermiform appendix in this volume. American contributions to colon surgery are prominently mentioned.

The impression is given of a rather thorough review of the literature by the author, possibly not quite sufficiently critical to help the untrained surgeon and offering little new material for those well trained.

THOMAS C. DOUGLASS.

THE first four chapters of *Diseases of the Urethra and Penis* by McCrea[2] are devoted to the anatomy, anomalies and congenital malformations. The discussion of gonorrhea is brief. For its treatment, four-foot Janet urethral "grand lavages" twice daily, and urethral instillations of 2 to 5 per cent protargol solution four times daily are recommended. "Definite value" was assigned to the use of vaccines in acute Neisserian infections. The sulphonamide group is mentioned, but the author feels it is too early to say whether or not the results claimed are unduly optimistic. In a series of 3270 patients with gonococcal urethritis treated at St. Luke's Hospital, Manchester, complicating epididymitis was noted in 253 patients, or 7.7 per cent. The treatment of acute epididymitis is given as either palliative or operative. A word on gonorrheal arthritis is included.

The subject of urethral strictures is well covered. Classification may be made according to their response to treatment. Surgical treatment of urethral strictures, including their resection, is illustrated in detail, and the treatment pitfalls are emphasized. The discussion of penile and urethral tumors and foreign bodies is adequate. There are many interesting photographs and a few colored drawings.

This volume sums up the bibliography and opinions of many foreign writers on diseases of the penis and urethra, thereby lending itself as a handy reference on these subjects.

LEANDER W. RIBA.

THE volume *L. Emmett Holt; Pioneer of a Children's Century*[3] is of distinct value in two different ways: first and most important perhaps, as a historical outline of the early history and growth of pediatrics as a medical specialty in this country, and second, as the biography of a late victorian physician in New York City. The authors have produced a readable and interesting work from these points of view. Because the subject matter is not particularly dramatic, it would probably interest a limited number of people. However, anyone interested in the history of medicine or in the medical life and manners of this period will enjoy reading it. I should imagine, however, that the sale of *The Care and Feeding of Children* will exceed and outlive its author's biography. A well tabulated index is included.

C. ANDERSON ALDRICH.

THE book *Hydrocephalus* by Marburg[4] is curiously confusing. One can excuse sentences the structures of which are more German than English; even such luxurious but lumpy terms as "hydrocephalus occlusis anterior of Guttmann," "subependymal luxuriation," and "transmineralization" can be managed by a patient reader. However, one gains the impression that the opinions expressed in this book have been formulated more through a critique of the work of others than by personal experience and observation by the author. One feels that possibly the author has a completely clear under-

[1] ABDOMINAL OPERATIONS. By Rodney Maingot, F.R.C.S.(Eng.). Vols. 1 and 2. New York and London: D. Appleton-Century Co., 1940.

[2] DISEASES OF THE URETHRA AND PENIS. By E. D'Arcy McCrea, M.D., M.Ch.(Dub.), F.R.C.S.I., F.R.C.S.(Eng.). Baltimore: The Williams & Wilkins Co., 1940.

[3] L. EMMETT HOLT; PIONEER OF A CHILDREN'S CENTURY. By R. L. Duffus and L. Emmett Holt, Jr. Foreword by Edwards A. Park, M.D. New York, London: D. Appleton-Century Co., 1940.

[4] HYDROCEPHALUS; ITS SYMPTOMATOLOGY, PATHOLOGY, PATHOGENESIS, AND TREATMENT. By Otto Marburg, M.D. New York: Oskar Piest, 1940.

standing of the nature of hydrocephalus but that he fails to clarify the mind of the reader after assaulting him with many controversial statements. The end-result is that the reader does not know whose opinion to respect.

The book abounds in surprising statements, examples of which follow: "I wish to emphasize that the increase of cerebrospinal fluid production is never a hypersecretory phenomenon." "The diagnosis of hydrocephalus is based upon ventriculography or encephalography." "My researches lead to the conclusion that hydrocephalus is produced by a disturbance of water metabolism." The author also states that he believes peripheral neuralgias to be caused by a hydration of the nerves. Epilepsy may be considered in the same light, so that there is a "common basis for different diseases, water metabolism and permeability of the barriers standing in the foreground."

This is armchair science, much too richly interlarded with the first person singular pronoun. It is unconvincing, unstimulating, and uninformative. The bibliography, not noteworthy for its freshness, is principally in German. JOHN MARTIN.

WRITTEN specifically for the medical corps of the British Army by a man who "has commanded almost every kind of Unit in the field on active service," *Organization, Strategy and Tactics of the Army Medical Service in War*[1] is a model of clarity and practical usefulness. Army and training regulations are often ponderous in size and style and many and various pamphlets and manuals would have to be collected to cover the material here so conveniently presented in one book. From the Regimental Medical Establishments all the way back to the problems of casualties in the home territory, each unit is succinctly described. For example, the Casualty Clearing Station (our Evacuation Hospital) is treated under the following headings: number mobilized, site, capacity, personnel, subdivisions of unit, notes on equipment, transport, load tables, time and space, organization, information, nonmedical factors, and duties. The general organization of the army and the recognized principles of war are discussed in their application to the medical corps. A very practical chapter on "The Appreciation of the Situation" covers what we American reserve officers study, using the word "Estimate" instead. Definite lists of the returns to be rendered and the forms to be used in hospitals will be appreciated by all who are new to such work. There is a chapter on the calculations of battle casualties with useful formulas. And since the first edition in 1937, there have been added a chapter on "The Transport of Casualties by Air," one on "The Anti-Aircraft Medical Services," and an entire section on "Medical Arrangements for Military Casualties at Home." Chapters on strategy and tactics and over 100 pages of problems and exercises are provided. As the word "Blitzkrieg" does not occur in the index and the preface is dated May, 1940, one can easily imagine that sweeping alterations and revisions will be called for in any future edition. The present text, however, planned and practically all written by one man, offers a unified, integrated and most convenient manual. It is to be hoped something similar may be written for the Medical Corps of the United States Army. JOHN FAVILL.

[1] ORGANIZATION, STRATEGY AND TACTICS OF THE ARMY MEDICAL SERVICES IN WAR. By Lieut.-Colonel T. B. Nichols, M.B., Ch.B. With chapters by A. S. Glynn, A. R. Laurie, and F. G. Lescher. 2d ed. London: Baillière, Tindall & Cox, 1940.

THE second edition of *Practical Handbook of the Pathology of the Skin*[2], which is a revision of Macleod's 1903 book, meets a very real need of the modern student of dermatology. It is an introduction to the histology, pathology, bacteriology, and mycology of the skin, with special reference to technique. The book is the outcome of the many years of personal experience and research of the authors, and they have also drawn freely from the accumulated knowledge of recent years scattered so widely over textbooks and journals.

Practically all of the common laboratory procedures used by the modern dermatologist are taken up separately and with minute instructive detail. We find the full and orderly discussion of biopsies, methods for the histological examination of skin material in the fresh state, methods of preserving skin material for histological examination, methods of imbedding, cutting and preparation for staining, and general principles of staining. Subsequently, as each group of diseases of the skin is taken up, the special staining techniques for that particular group of pathological changes is given and discussed in detail.

The anatomy, embryology, and physiology of the skin, its components, and its various appendages are all reviewed with interest and thoroughness. The separate diseases of the skin are logically classified and the important elementary facts are given. The description of disease changes is alive and dynamic, and it is based on our present day academic knowledge as well as on a discussion of what is to be seen in the dead section of tissue.

The chapters devoted exclusively to bacterial, plant, and animal parasites of the skin are 51 pages in length. They include many illustrations of great teaching value, an identification table of 15 of the common ringworm fungi, and a discussion of media and cultural methods. JULIUS E. GINSBERG.

[2] PRACTICAL HANDBOOK OF THE PATHOLOGY OF THE SKIN; AN INTRODUCTION TO THE HISTOLOGY, PATHOLOGY, BACTERIOLOGY AND MYCOLOGY OF THE SKIN WITH SPECIAL REFERENCE TO TECHNIQUE. By J. M. H. Macleod, M.A., M.D., F.R.C.P.(Lond.), and I. Muende, M.B., B.S., B.Sc.(Lon.). 2d ed. New York: Paul B. Hoeber, Inc., 1940.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

MACLEOD'S PHYSIOLOGY IN MODERN MEDICINE. Edited by Philip Bard, et al. 9th ed. St. Louis: The C. V. Mosby Co., 1941.

TRANSACTIONS OF THE AMERICAN GYNECOLOGICAL SOCIETY. Volume 65 for the Year 1940. Edited by Richard W. TeLinde, M.D. St. Louis: The C. V. Mosby Co., 1941.

HEMORRHAGIC DISEASES; PHOTO-ELECTRIC STUDY OF BLOOD COAGULABILITY. By Kaare K. Nygaard, M.D. St. Louis: The C. V. Mosby Co., 1941.

MANUAL OF CLINICAL CHEMISTRY. By Miriam Reiner, M.Sc. New York: Interscience Publishers, Inc., 1941.

HANDBOOK OF ANAESTHETICS. Revised by R. J. Minnitt, M.D. (Liverpool), D.A. (R.C.P. & S. Eng.). Baltimore: The Williams and Wilkins Co., 1940.

PERIODICITY AND CAUSE OF CANCER, LEUKAEMIA AND ALLIED TUMOURS. By J. H. D. Webster, M.D., F.R.C.P.E., F.F.R. Baltimore: The Williams & Wilkins Co., 1940.

SPERMATOZOA AND STERILITY. By Abner I. Weisman, M.D. New York and London: Paul B. Hoeber, Inc., 1941.

BEHANDLUNG RHEUMATISCHER ERKRANKUNGEN DURCH ANAESTHESIE. By Dr. Egon Fenz. Dresden and Leipzig: Theodor Steinkopff, 1941.

RHEUMATISMUS UND FRAUENKRANKHEITEN. By Professor Dr. Heinz Küstner. Dresden and Leipzig: Theodor Steinkopff, 1941.

PHARMACOLOGY. By J. H. Gaddum, Sc.D., M.R.C.S., L.R.C.P. London and New York: Oxford University Press, 1940.

APPLIED PHYSIOLOGY. By Samson Wright, M.D., F.R.C.P. London and New York: Oxford University Press, 1940.

NATURAL RESISTANCE AND CLINICAL MEDICINE. By David Perla, B.S., M.D. and Jessie Marmorston, B.S., M.D. Boston: Little, Brown & Co., 1941.

PROCEEDINGS OF THIRTY-FOURTH ANNUAL CONVENTION OF THE ASSOCIATION OF LIFE INSURANCE PRESIDENTS. N. Y.: The Association of Life Insurance Presidents, 1940.

MERCHANTS IN MEDICINE. By Emanuel M. Josephson, M.D., New York: Chedney Press, 1941.

FOCUS ON AFRICA. By Richard Upjohn Light. New York: American Geographical Society, 1941.

ROENTGEN INTERPRETATION. By George W. Holmes, M.D. and Howard E. Ruggles, M.D. Philadelphia: Lea & Febiger, 1941.

THE THERAPEUTICS OF INTERNAL DISEASES. Edited by George Blumer, M.A., M.D., and Albert J. Sullivan, M.D. Vol. 3. New York: D. Appleton-Century Co., Inc., 1941.

FIRST AID IN EMERGENCIES. By Eldridge L. Eliason, A.B., M.D., Sc.D., F.A.C.S. 10th ed. Philadelphia, Montreal and London: J. B. Lippincott Co., 1941.

APPROVED LABORATORY TECHNIC; CLINICAL PATHOLOGICAL, BACTERIOLOGICAL, MYCOLOGICAL, PARASITOLOGICAL, SEROLOGICAL, BIOCHEMICAL AND HISTOLOGICAL. By John A. Kolmer, M.S., M.D., and Fred Boerner, V.M.D. 3d ed. New York: D. Appleton-Century, Inc., 1941.

CORRESPONDENCE

THE PAN-AMERICAN LEAGUE AGAINST CANCER

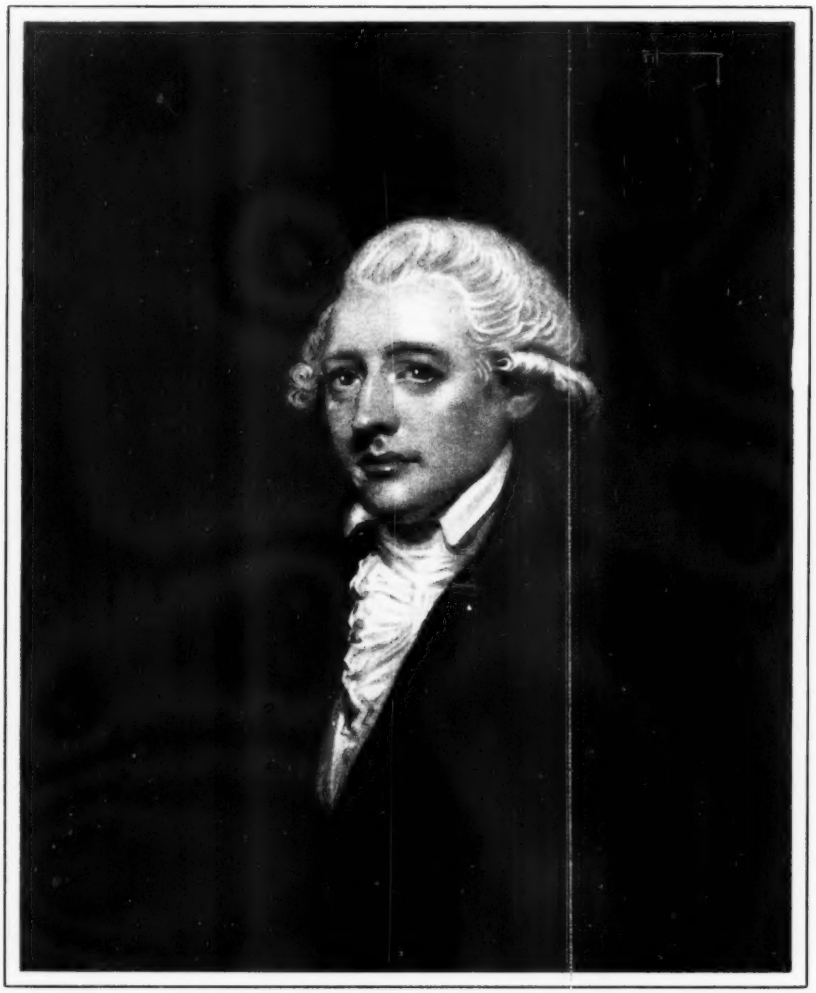
THE Pan-American League against Cancer was organized recently in the state of New York, to carry on in the Western Hemisphere the scientific and social work of the International Union against Cancer. Professor Francis Carter Wood, of New York, Professor Angel H. Roffo, of Buenos Aires, and Mr. Boris Fregel, respectively, vice-president, member of the board of directors, and president of the finance committee of the International Union against Cancer, with the co-operation of other outstanding personalities in the field of cancer, were active in the organization of this society.

The aims of the organization, as outlined in the certificate of incorporation are: (a) to promote and encourage the international fight against cancer; (b) to co-ordinate in the countries of the American continents the scientific study and research in cancer, and to publish and disseminate information thereon; (c) to engage in social welfare work in its relation to the problem of cancer; (d) to promote the establishment of national organizations throughout the Western Hemisphere to engage in similar activities.

It is hoped to include in its comprehensive program: (a) the publication of a Pan-American cancer journal; (b) the organization and maintenance of a Pan-American center of information and statistics on cancer; (c) the establishment of a Pan-American system of fellowships, scholarships, endowments, and exchange of scholars and students; and (d) the immediate organization of a First Pan-American Cancer Week to be held simultaneously in forty countries throughout the world; the holding of a Pan-American Congress for the Scientific and Social Fight against Cancer, probably in Buenos Aires in 1942.

Further information about this League may be had by addressing Professor Francis Carter Wood, St. Luke's Hospital, Amsterdam Avenue and 116th Street, New York, New York.

WILLIAM CUMBERLAND CRUIKSHANK (1745–1800). Neighbor of Charles Bell, Kosciusko, Hogarth, and Joshua Reynolds in Leicester Square; successor to John Hunter as lecturer in anatomy at medical school in Windmill Street; Hunter's equal as an operating surgeon but lacked Hunter's surgical judgment; author of "Anatomy of Absorbing Vessels of Human Body."



William Cumberland Cruikshank

1745-1800